

UNIVERSITY of
STIRLING



**ELECTRONIC CIGARETTES FOR
SMOKERS WITH
SCHIZOPHRENIA SPECTRUM
DISORDERS**

Pasquale Caponnetto
Student number: 2431558
Submitted for the degree of Doctor of Philosophy
Faculty of Health Sciences and Sport
University of Stirling
3 September 2019

ABSTRACT

Tobacco use is the greatest threat to public health worldwide, killing more than seven million people annually. Globally, people with schizophrenia smoke disproportionately more than the general population and those with other mental illnesses. Consequently, they carry the burden of smoking-attributable morbidity and premature mortality. The risk of serious disease diminishes rapidly after stopping smoking and life-long abstinence is known to reduce the risk of lung cancer, heart disease, stroke, chronic lung disease and other cancers.

This research involved three novel contributions to the literature. First, a qualitative study was conducted with 30 current smokers with schizophrenia spectrum disorders, some motivated to stop smoking and others with no intention to quit. This study explored their views regarding traditional cigarettes compared with e-cigarettes and licensed cessation aids or e-cigarettes for smoking cessation or smoking reduction. In interviews, about half of participants (16 of 30) reported an interest in using e-cigarettes to quit or reduce smoking. Of these, four were from the less motivated group, suggesting that e-cigarettes may appeal to schizophrenic smokers not currently considering cessation.

Secondly, a quantitative, prospective single-arm pilot study was conducted that investigated the role of e-cigarettes in smoking cessation or reduction for smokers with schizophrenia spectrum disorders. Forty smokers were recruited and 37 of these completed the study. Sixteen participants were CO verified as abstinent from smoking at the end of the study (40%) and 21 (52.5%) significantly reduced their cigarette consumption. The e-cigarette and study procedures were deemed feasible and acceptable to participants. Some adverse events were noted but were rare.

Finally, building on these earlier studies, a full protocol for a large multicenter randomised controlled study with long term follow-up was prepared. This protocol could guide the development of a research proposal for a future trial.

KEY WORDS

Smoking, e-cigarette, smoking cessation, smoking reduction, schizophrenia

TABLE OF CONTENTS

| | |
|--|-----------|
| LIST OF FIGURES | 10 |
| LIST OF TABLES | 11 |
| LIST OF PHOTOGRAPHS | 12 |
| LIST OF ABBREVIATIONS | 13 |
| ACKNOWLEDGMENTS | 15 |
| STATEMENT OF ORIGINAL AUTHORSHIP | 16 |
| | |
| CHAPTER 1: INTRODUCTION TO MENTAL HEALTH AND SMOKING | 17 |
| 1.1 Aim and objectives | 17 |
| 1.2 Methodology | 18 |
| 1.3 Structure of thesis | 18 |
| 1.4 Epidemiology of tobacco smoking and related harm among the general population | 19 |
| 1.5 Epidemiology of tobacco smoking and related harm in the mental health population | 23 |
| 1.5.1 Prevalence of smoking | 23 |
| 1.5.2 Smoking behaviour | 24 |
| 1.5.3 Effect of smoking on the mortality and physical health of people with schizophrenia spectrum disorders | 26 |
| 1.5.4 Effect of smoking on the mental health of people with schizophrenia spectrum disorders | 27 |
| | |
| 1.6 Schizophrenia spectrum disorders: symptomatology, diagnostic criteria, prognosis, aetiology and principal treatments | 29 |
| 1.7 Theory explaining high smoking rates and high nicotine dependence in smokers with schizophrenia spectrum disorders | 35 |
| 1.7.1 Illness-related factors | 36 |
| 1.7.2 Patient-related factors | 38 |
| 1.7.3 Health service- and health professionals-related factors | 40 |
| 1.8 Motivation to quit smoking in the general population and motivation to quit smoking in people with schizophrenia spectrum disorders | 41 |

| | |
|--|-----------|
| 1.9 Smoking cessation treatments in the general population | 43 |
| 1.10 Smoking cessation treatments for people with schizophrenia spectrum disorders | 46 |
| 1.11 Summary and conclusion | 53 |
| | |
| CHAPTER 2: INTRODUCTION TO E-CIGARETTES | 55 |
| 2.1 Tobacco harm reduction | 55 |
| 2.2 E-cigarettes | 56 |
| 2.2.1 E-cigarette market and types | 57 |
| 2.2.2 The JUUL e-cigarette | 59 |
| 2.2.3. Existing evidence on e-cigarette harms and benefits | 60 |
| 2.3.3.1 <i>Recent studies on relative risks in comparison with smoking</i> | 61 |
| 2.3 E-cigarette use and craving | 65 |
| 2.4 E-cigarettes and smoking cessation | 66 |
| 2.4.1 Early studies of e-cigarettes for smoking cessation | 67 |
| 2.4.2 Systematic reviews of e-cigarettes for smoking cessation | 69 |
| 2.4.3 More recent studies of e-cigarettes for smoking cessation | 72 |
| 2.5 E-cigarettes for smoking cessation in people with schizophrenia spectrum disorders | 74 |
| 2.5.1 Interventional studies | 74 |
| 2.5.2 Prevalence and attitudes towards e-cigarettes in people with schizophrenia spectrum disorders | 76 |
| 2.6 Summary and conclusion | 78 |
| | |
| CHAPTER 3: QUALITATIVE STUDY | 80 |
| 3.1 Study title: A qualitative study of the views about smoking, licensed cessation aids and e-cigarettes in people with schizophrenia spectrum disorders | 80 |
| 3.2 Chapter overview | 80 |
| 3.3 Purpose of the study | 80 |
| 3.4 Research questions | 81 |
| 3.5 Methodology | 81 |
| 3.6 Methods | 83 |
| 3.6.1 Eligibility criteria | 83 |

| | | |
|--|---|------------|
| 3.6.2 | Setting | 85 |
| 3.6.3 | Sampling and recruiting strategy | 86 |
| 3.6.4 | Ethical issues | 86 |
| 3.6.5 | Data collection and processing | 87 |
| 3.6.6 | Analysis | 89 |
| 3.6.7 | Data management | 91 |
| 3.7 | Findings | 91 |
| 3.7.1 | Participant characteristics | 91 |
| 3.7.2 | Themes | 93 |
| 3.7.2.1 | <i>Theme 1: Reasons for starting to smoke</i> | 93 |
| 3.7.2.2 | <i>Theme 2: Perceptions of traditional cigarettes compared with e-cigarettes</i> | 94 |
| 3.7.2.3 | <i>Theme 3: Perceptions and appeal of licensed medication for smoking cessation or reduction</i> | 99 |
| 3.7.2.4 | <i>Theme 4: The appeal of e-cigarettes for smoking cessation or reduction</i> | 102 |
| 3.8 | Discussion | 103 |
| 3.9 | Reflexivity | 111 |
| 3.10 | Conclusion | 117 |
| CHAPTER 4: FEASIBILITY AND SINGLE ARM PILOT STUDY | | 118 |
| 4.1 | Study title: Role of an electronic cigarette in smoking cessation or reduction for smokers with schizophrenia spectrum disorders: a feasibility and pilot single arm study | 118 |
| 4.2 | Background and objectives | 118 |
| 4.3 | Research questions | 120 |
| 4.4 | Methods | 120 |
| 4.4.1 | Study design | 120 |
| 4.4.2 | Study team | 120 |
| 4.4.3 | Ethics | 121 |
| 4.4.4 | Participants | 121 |
| 4.4.5 | Inclusion criteria | 121 |
| 4.4.6 | Exclusion criteria | 122 |
| 4.4.7 | Recruitment | 122 |

| | | |
|---|--|------------|
| 4.4.8 | Procedures | 123 |
| 4.4.9 | Outcomes | 126 |
| 4.4.10 | Statistical analysis | 127 |
| 4.5 | Results | 128 |
| 4.5.1 | Participant characteristics | 128 |
| 4.5.2 | Changes in smoking behaviour | 131 |
| 4.5.2.1 | <i>Smoking cessation</i> | 131 |
| 4.5.2.2 | <i>Smoking reduction</i> | 131 |
| 4.5.3 | Adoption rate and adherence to product use | 133 |
| 4.5.4 | Acceptability | 133 |
| 4.5.4.1 | <i>Vital signs (blood pressure and HR) and weight</i> | 134 |
| 4.5.4.2 | <i>Psychopathological changes during e-cigarette use</i> | 134 |
| 4.5.4.3 | <i>Adverse events</i> | 135 |
| 4.5.4.4 | <i>Subjective effects</i> | 135 |
| 4.6 | Discussion | 137 |
| 4.6.1 | Outcomes in relation to the research questions | 138 |
| 4.6.2 | Contribution of the PhD candidate | 141 |
| 4.6.3 | Limitations | 142 |
| 4.6.4 | Future research | 143 |
| 4.7 | Conclusion | 144 |
| CHAPTER 5: ROLE OF AN ELECTRONIC CIGARETTE IN SMOKING CESSATION OR REDUCTION FOR SMOKERS WITH SCHIZOPHRENIA SPECTRUM DISORDERS: A PROTOCOL FOR A LARGE MULTICENTER RANDOMISED CONTROLLED TRIAL | | 145 |
| 5.1 | Title and Summary | 148 |
| 5.2 | Methods | 149 |
| 5.2.1 | Trial design | 149 |
| 5.2.2 | Participants | 149 |
| 5.2.3 | Ethics | 150 |
| 5.2.4 | Interventions | 150 |
| 5.2.5 | Study procedures | 154 |
| 5.2.6 | Study discontinuation | 158 |
| 5.2.7 | Outcomes | 159 |

| | | |
|------------------------------|--|------------|
| 5.2.8 | Sample size | 160 |
| 5.2.9 | Randomisation | 161 |
| 5.2.10 | Statistical methods | 161 |
| 5.2.11 | Study plan | 163 |
| 5.2.12 | Next steps | 163 |
| CHAPTER 6: DISCUSSION | | 164 |
| 6.1 | Summary of the research | 165 |
| 6.2 | Perspectives on smoking and e-cigarettes amongst people with schizophrenia spectrum disorders | 165 |
| 6.3 | E-cigarettes for smoking cessation and reduction in people with schizophrenia spectrum disorders | 169 |
| 6.4 | Reflections on the qualitative and quantitative research and implications for the proposed future RCT | 172 |
| 6.4.1 | Emerging implications | 176 |
| 6.5 | Strengths and limitations | 177 |
| 6.5.1 | Strengths | 177 |
| 6.5.2 | Limitations | 178 |
| 6.6 | Reflection on my role in the research | 179 |
| 6.7 | Implications for the intervention by a large multisite randomised controlled trial with long-term follow-up and for clinical practice | 180 |
| 6.8 | Implications for future research | 180 |
| 6.9 | Conclusion | 181 |
| REFERENCES | | 183 |
| APPENDICES | | 217 |
| Appendix 1: | Ethics approval, qualitative study | 217 |
| Appendix 2: | Information sheet for patients, qualitative study | 218 |
| Appendix 3: | Participant consent form, qualitative study | 220 |
| Appendix 4: | Structured interview | 221 |
| Appendix 5: | Example of transcript and coding | 224 |
| Appendix 6: | Ethics approval, quantitative study | 237 |

| | | |
|---------------------|---|------------|
| Appendix 7: | Health care provider contact record, quantitative study | 238 |
| Appendix 8: | Flyer, qualitative study | 239 |
| Appendix 9: | Health provider information, qualitative study | 240 |
| Appendix 10: | Patient information sheet and consent form, qualitative study (Italy and US sites) | 241 |
| Appendix 11: | Fagerström Test for Cigarette Dependence – Revised (FTCD) | 259 |
| Appendix 12: | Scale for the Assessment of Negative Symptoms (SANS) | 260 |
| Appendix 13: | Scale for the Assessment of Positive Symptoms (SAPS) | 275 |
| Appendix 14: | Modified Cigarette Evaluation Questionnaire (mCEQ), adapted for e-cigarette users | 300 |
| Appendix 15: | Symptoms and adverse events (AE) form | 301 |

LIST OF FIGURES

| | |
|---|------------|
| Figure 1: Evolution in e-cigarettes models | 59 |
| Figure 2: JUULe-cigarette | 59 |
| Figure 3: Six-phased guide suggested by Braun & Clarke | 91 |
| Figure 4: Study flowchart | 129 |
| Figure 5: Changes in smoking behaviour at week 12 | 132 |
| Figure 6: First generation e-cigarette versus JUUL e-cigarette | 141 |
| Figure 7: Study diagram | 154 |

LIST OF TABLES

| | | |
|------------------|--|------------|
| Table 1: | Examples of qualitative methodologies | 82 |
| Table 2: | Characteristics of participants | 92 |
| Table 3: | Themes and codes | 93 |
| Table 4: | Participants' characteristics | 130 |
| Table 5: | Participants' traditional cigarette consumption at baseline and at 12 weeks | 131 |
| Table 6: | Smoking behaviour outcomes | 132 |
| Table 7: | Participants' vital signs, weights and psychopathological changes from baseline to week 12 | 134 |
| Table 8: | Adverse effects reported by participants | 135 |
| Table 9: | Subjective effects of e-cigarettes: Participant responses to mCEQ questions n (%) | 136 |
| Table 10: | How key elements of the qualitative and single arm pilot study informed the protocol for a future RCT | 145 |
| Table 11: | Behaviour change techniques (BCTs) applicated | 153 |
| Table 12: | Study schedule/flowchart | 158 |

LIST OF PHOTOGRAPHS

| | |
|---|------------|
| Smoker's Fingers | 115 |
| Smoker's Clothing | 115 |
| Garden at the Schizophrenia Center | 115 |
| Stairs at the Schizophrenia Center | 115 |
| Waiting room at the Schizophrenia Center (1) | 116 |
| Waiting room at the Schizophrenia Center (2) | 116 |
| Curtain of the waiting room | 116 |

LIST OF ABBREVIATIONS

| | |
|--------|--|
| AEs | Adverse events |
| ANOVA | Analysis of variance |
| APA | American Psychiatric Association |
| aPR | Adjusted Prevalence Ratio |
| BACS | Brief assessment of cognition in schizophrenia |
| BCT | Behaviour change technique |
| BL | Baseline |
| BP | Blood pressure |
| CBT | Cognitive behavioral therapy |
| CI | Confidence interval |
| CO | Carbon monoxide |
| COPD | Chronic obstructive pulmonary disease |
| CPCT | Smoking cessation center of Catania University (Centro per la Prevenzione e Cura del Tabagismo) |
| CPD | cigarettes/day |
| CRF | Case report form |
| CVDs | Cardiovascular diseases |
| CYP | Cytochrome P450 |
| DSM-V | Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition |
| EAGLES | Evaluating Adverse Events in a Global Smoking Cessation |
| eCO | Exhaled carbon monoxide |
| ENDS | Electronic Nicotine Delivery Systems |
| EQ VAS | Quality of life scale by VAS EuroQol Group |
| ET | Early termination visit |
| FCTC | World Health Organization Framework Convention on Tobacco Control |
| FDA | Food and Drug Administration |
| FTCD | Fagerström Test for Cigarette Dependence |
| HR | Heart rate |
| ICD | International Classification of Diseases |
| IQR | Interquartile range |

| | |
|---------|---|
| IRB/IEC | Institutional Review Board/Independent Ethics Committee |
| ISTAT | National Institute of Statistics (Istituto Nazionale di Statistica) |
| mCEQ | Modified Cigarette Evaluation Questionnaire |
| MTSS | Motivation to Stop Scale |
| nAChRs | Nicotine acetylcholine receptors |
| NICE | National Institute for Health and Care Excellence |
| NIMH | National Institute of Mental Health |
| NNAL | 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol |
| NNK | 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone |
| NRT | Nicotine replacement therapy |
| OSSFAD | Osservatorio Droga Alcol e Fumo |
| OR | Odds ratio |
| PANSS | Positive and Negative Syndrome Scale |
| PIS | Patient information sheets |
| QALY | Quality-adjusted life year |
| RBANS | Repeatable Battery for the Assessment of Neuropsychological Status |
| RCP | Royal College of Physicians |
| RCT | Randomised controlled trial |
| RR | Relative Risk |
| RRP | Reduced risks products |
| SAEs | Serious adverse events |
| SANS | Scale for Assessment of Negative Symptoms |
| SAPS | Scale for Assessment of Positive Symptoms |
| SD | Standard deviation |
| SMR | Standardised mortality ratio |
| SPSS | Statistical Package for Social Sciences Program |
| SSN | Servizio Sanitario Nazionale |
| THR | Tobacco harm reduction |
| TSNAs | Tobacco-specific N-nitrosamines |
| UCDC | Department of Health and Human Services |
| WHO | World Health Organization |

ACKNOWLEDGMENTS

My thanks and appreciation to the individuals I encountered in the schizophrenia treatment center cannot be expressed in words. For the smokers with schizophrenia spectrum disorders, participants or not, whose thoughts helped to mould the study discussed in this thesis, thanks to you, and your significant others, for letting me into your lives. To all the individuals working with people affected by serious mental illness, smokers and nonsmokers, thank you for helping these vulnerable people.

Many thanks to my two professors who supervised my PhD at various stages, Professor Linda Bauld and Dr Deborah Robson, and their refreshing views on behavioural approaches to improving public health, especially their approach to qualitative and quantitative research.

Credit must be given to my “Master” at the University of Catania, “Centro per la Prevenzione e Cura del Tabagismo-CPCT”, Prof Riccardo Polosa (Full Professor of Internal Medicine), for patiently listening to me, even though this work based also on psychopathology is so different to his background. And to my colleagues many thanks for your ideas, inspirations, love, support and practical tips; I love you all.

A never-ending gratitude to all my family and smokers I helped during my last 15 years of work at the smoking cessation center of Catania University-CPCT, those I’ve lost and gained over the years of this work, for their continuous support; love you all. To my precious four children, Antonio, Carolina, Costanza and Aurelio, who did not cause much distraction from my research. And to my “amore”, for her patience with me.

And last, but certainly not least, my cancer for instilling resilience in me from 2006.

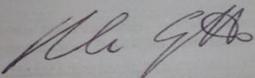
This thesis is dedicated to the men of the 51st Highland Division.

STATEMENT OF ORIGINAL AUTHORSHIP

I hereby declare that this thesis embodies the results of my own research and that I am the full author of this thesis, except where otherwise stated, and that it has been submitted only for the degree of PhD in the University of Stirling.

Signed:

Dr Pasquale Caponnetto



Date: 03 September 2019

CHAPTER 1: INTRODUCTION TO MENTAL HEALTH AND SMOKING

This thesis focuses on the topic of electronic cigarettes (e-cigarettes) for smokers with schizophrenia spectrum disorders. This introductory chapter on mental health and smoking outlines the aim and objectives of the research, introduces the research methods employed and outlines the structure of the thesis. It provides the background to the topic in terms of a) epidemiology of tobacco smoking and related harm amongst the general population; b) epidemiology of tobacco use and related harm in the mental health population; c) symptomatology, diagnostic criteria, prognosis, aetiology and principal treatments of schizophrenia; d) theory explaining high smoking rates and high nicotine dependence in smokers with schizophrenia; e) motivation to quit smoking in both the general population and people with schizophrenia spectrum disorders; f) smoking cessation treatments in the general population and g) smoking cessation treatments for people with schizophrenia spectrum disorders. It concludes with comments on the significance of the research and why it constitutes an original contribution.

1.1 Aim and objectives

The main aim of this thesis is to inform the development of future studies to assess the potential role of e-cigarettes for smoking cessation or reduction for smokers with schizophrenia spectrum disorders. The research studies in the thesis aimed to explore whether e-cigarettes are acceptable and feasible for smoking cessation in this high priority group.

The objectives of this thesis are to:

- 1:** Examine the existing literature to inform the design, conduct and interpretation of research on e-cigarettes for smoking cessation or reduction in smokers with schizophrenia spectrum disorders.
- 2.** Explore the perceptions of smokers with schizophrenia spectrum disorders regarding licensed smoking cessation treatments and e-cigarettes.
- 3:** Investigate the feasibility and acceptability of e-cigarettes for smoking cessation or reduction in smokers with schizophrenia spectrum disorders

4: Develop plans for future research on this topic, including a protocol for a future multi-site randomised controlled trial (RCT) with longer term follow up.

1.2 Methodology

The present research employed a mixed design, involving both qualitative and quantitative methods. In stage one, using qualitative structured interviews, the perceptions of licenced treatments and e-cigarettes for smoking cessation or smoking reduction were explored amongst 30 people with schizophrenia spectrum disorders who were current smokers. In stage two, a quantitative single-arm pilot study with 40 smokers with schizophrenia spectrum disorders, who were not motivated to quit, explored the efficacy, acceptability and feasibility of an e-cigarette intervention. Both studies were conducted with patients who were receiving care from the local Department of Mental Health of the Italian National Health System (Servizio Sanitario Nazionale (SSN)). Stage three involved reflecting on this research and developing a protocol for a future RCT.

1.3 Structure of the thesis

This PhD thesis includes six chapters. Details of the remaining chapters are as follows.

Chapter two introduces the concepts of tobacco harm reduction (THR) and includes a review of relevant literature on e-cigarettes and on the potential effectiveness of e-cigarettes as an emerging approach to smoking cessation in the general population and amongst patients with schizophrenia.

Chapter three focuses on the first empirical study in the PhD. It describes the methods and findings of a qualitative study with 30 smokers with a schizophrenia spectrum disorder. It examines their perceptions of smoking traditional cigarettes, the appeal of licensed aids for smoking cessation or smoking reduction, and the appeal of e-cigarettes for smoking cessation or smoking reduction. The experiences of participants who are motivated to quit are compared with those who are not motivated to quit. The chapter includes a discussion about researcher reflexivity and limitations of the study.

Chapter four describes methods and findings from a (quantitative) single arm pilot study with 40 smokers with a schizophrenia spectrum disorder to evaluate the feasibility and acceptability of e-cigarettes for smoking cessation or reduction. It details the approach to the research and the hypotheses tested. The chapter also includes a discussion of the study hypotheses and significance, the contribution of the PhD candidate, limitations of the study and indications for future research.

Chapter five includes a full protocol for a future large RCT to evaluate the efficacy of e-cigarettes on smoking cessation or reduction for smokers with schizophrenia spectrum disorders. The chapter has the main elements of a standard protocol, including title and abstract, introduction, objectives, and methods. Methods include trial design, participants, ethics, interventions, products tested, outcomes, sample size, randomisation and statistical methods.

Finally, chapter six discusses and aims to interpret the findings of this research in the context of the wider literature. Strengths and limitations of the present work are also presented here. The chapter concludes with implications of the thesis findings for clinical practice in the area of mental health tobacco control and suggestions for related future research.

1.4 Epidemiology of tobacco smoking and related harm amongst the general population

Amongst the World Health Organization (WHO) regions, in 2015, over 1.1 billion people smoked tobacco. Far more males (36.1%) than females (6.8%) smoked tobacco. Although it is declining worldwide and in many countries, the prevalence of tobacco smoking appears to be increasing in the WHO Eastern Mediterranean Region and the African Region. Amongst the WHO regions (Europe, Western Pacific, Eastern Mediterranean, America, South-East Asia, and Africa) Europe has the highest prevalence of tobacco smoking amongst adults (28%) (WHO, 2018).

In Italy, adult smoking prevalence has consistently decreased since recording started in 1957 (Gallus et al., 2013). From 2013 to 2014, Lugo et al. (2015) found an overall smoking prevalence amongst Italian adults of 21% (26% of men and 17% of women). This agrees with recent data from a large household survey (based on 60,000 families and 130,000 individuals) conducted in 2013 by the

National Institute of Statistics (ISTAT), showing an adult smoking rate of 21% (26% in men and 16% in women) (ISTAT, 2015). Another study confirmed the decreasing trend observed over the last five decades in men and over the last two decades in women (Gallus et al., 2013). However, no significant decrease in terms of smoking prevalence has been observed in men or women between 2007 and 2014. This likely reflects the lack of adoption of effective and relevant additional antismoking measures after the successful ban introduced in 2005 (Joossens & Raw, 2013) and smoking prevalence has levelled off over the last few years (OSSFAD (Osservatorio Droga Alcol e Fumo), 2016). In 2005 the Italian government banned smoking in all indoor public places, including offices, cafes, restaurants (except for a few with separate and regulated smoking areas), airports, and railway stations. Italy was the first large country in Europe to introduce a comprehensive smoking ban, which resulted in a further acceleration of the decreasing trend of smoking prevalence in both sexes (Gallus et al., 2006; Tramacere et al., 2009; ISTAT, 2015). In February 2016, the Italian government established new legislation regarding tobacco smoking. New anti-smoking laws have imposed large fines for several offences and make it illegal to smoke in a car carrying children or pregnant women. The laws require cigarette packs to carry health warnings about the effects of smoking. Smoking is also prohibited outdoors near schools and hospitals. Tobacconists caught selling cigarettes to minors risk heavy fines and losing their license. Throwing cigarette butts on the pavement could cost an offender up to 300 Euros (OSSFAD, 2016). However, after the positive initial effects of the law of 2005, the prevalence of smokers in Italy has not decreased further and has instead remained static (OSSFAD, 2018).

Smoking traditional cigarettes is one of the largest risk factors for premature mortality from non-communicable diseases in the general population (Stringhini et al., 2017). Tobacco use is the greatest threat to public health worldwide, killing more than seven million people each year (WHO, 2017). Cigarette smoking is the single most preventable cause of death and disease. Smoking-related death is principally caused by lung and other cancers, ischemic heart disease and chronic obstructive pulmonary disease (COPD) (WHO, 2012; Doll et al., 2004). The risk of serious disease has been shown to diminish rapidly after smoking cessation – ‘quitting’ – and permanent abstinence markedly reduces the risk of lung cancer

and other cancers, ischemic heart disease and COPD. Considering that the main types of these non-communicable diseases are cardiovascular diseases (CVDs), cancers and chronic respiratory diseases, helping traditional cigarette smokers quit and remain abstinent is one of the most effective ways we can improve the public health of Italy, UK and the rest of the world. The associations between traditional cigarette smoking and hazards to physical health are described below.

Cigarette smoking is probably the most complex and the least understood amongst the risk factors for CVDs. Cigarette smoke contains several thousand chemicals, though there isn't concordance about the exact number of chemicals. Two studies report traditional cigarettes contain ≈ 4000 different chemicals with sizes ranging from atoms to particulate matter (Burns, 1991; Zemmann, 2011) and other two more recent papers demonstrate tobacco smoke contains more than 7000 chemicals (Perfetti & Rodgman, 2013; Tobacco Atlas, 2015). Individual smoking behaviour, intensity of smoking and the brand of cigarettes smoked further modulate the amount, number, and type of chemicals in tobacco smoke to which an individual is exposed (Conrad, 2011). Importantly, it is likely that it is not just a single compound or a compound class, such as oxidants, but rather a highly complex and changing mixture of compounds that is responsible for disease initiation, progression, and cardiovascular outcome. The interplay of these compounds with the individual's genetic background and the environment defines the onset, location, and pace of CVDs. For the past few decades, it has been clear that smoking is an important (and modifiable) risk factor for CVDs; according to WHO data, smoking is responsible for 10% of all CVD cases (WHO, 2012). However, for a long time it remained unclear how smoking causes CVDs. In 1993, Celermajer et al. (1992) published a study showing that smoking reduces flow-mediated dilatation (FMD) in systemic arteries in healthy young adults. Smoking not only plays a strong role in CVD initiation, but also significantly contributes to and causes disease progression and fatal cardiovascular outcomes. Current data clearly show that secondhand smoking can also trigger life-threatening conditions. Management and prevention of CVDs is a public health priority, and a simple intervention such as smoking cessation could lead to reduced prevalence of cardiovascular risk factors and, therefore, CVD itself.

There is a clear link between smoking initiation and cancer in later life. Smoking causes more than 48% of deaths from the 12 types of cancer caused by smoking. Smoking causes more than 80% of lung cancer deaths as well as 77% of larynx cancer deaths (Siegel et al., 2015). Approximately 168,000 people in the United States are estimated to die of cancer due to smoking each year. Continued progress in reducing cancer mortality will require more comprehensive tobacco control, including targeted cessation support (de Marco et al., 2004; Siegel et al., 2015). In Europe, the incidence of lung cancer ranges from eight to 62 per 100,000 persons, while prevalence ranges from 26 to 242 per 100,000 persons (Jimenez-Ruiz et al., 2011). In Europe, death rates from lung cancer increased by 58% between 1960 and 1988, but they declined by 14% in 1998, mainly due to the decreased incidence and mortality in males (Ezzati et al., 2003). The risk of developing lung cancer seems to be affected by the duration of smoking and the number of cigarettes (or cigars, or pipes) smoked daily (La Vecchia et al., 2003). The relative risk (RR) ratio between the occurrence of lung cancer amongst smokers and nonsmokers is 15 overall and 25 for heavy smokers (Doll et al., 2004). Reducing the intake of traditional cigarettes smoked per day may support a harm reduction approach but the US Cancer Prevention Study II has shown that the number of years of tobacco smoking is far more critical in predicting lung cancer risk than the number of cigarettes smoked daily (Alberg & Samet, 2003). The age of starting smoking increases lung cancer risk (Flanders et al., 2003); hence, promoting interventions to avoid smoking initiation (typically during the adolescence) are important.

Smoking is also the main cause of many respiratory diseases (UCDC, 2004). COPD is predicted to become the third leading cause of death in 2030 (WHO, 2008). Cigarette smoking is the most important risk factor for COPD and it can also promote the onset of exacerbations (Wedzicha & Donaldson, 2003). Data collected in European countries show that self-reported diagnosis of chronic bronchitis/emphysema (Viegi et al., 1999) or spirometry signs of airflow obstruction (Lundback et al., 2003) are more frequent in smokers than nonsmokers. The risk of developing COPD may be increased not only by the average daily number of cigarettes smoked but even more by cumulative pack-years (Viegi et al., 1999). Moreover, a study has shown that smokers with COPD have higher tobacco consumption, higher CO levels in exhaled air and higher dependence on nicotine

than healthy smokers (Lundback et al., 2003). However, despite COPD being considered as a smoking-related lung disorder, not all traditional cigarette smokers develop this disease. Faner et al. (2014) showed that some smokers may develop irreversible lung obstruction, which is linked with their epigenetic and genetic background (DeMeo et al., 2004) but smoking cessation plays a central role in COPD avoidance.

Cigarette smoking is also a risk factor for male and female sexual and reproductive dysfunctions. In particular, it is a risk factor for the onset of erectile dysfunction and traditional cigarettes contain elements that exert a direct harmful effect on male and female germ cells and embryos (Zenzes et al., 2000). Tobacco use amongst women during their reproductive years is especially dangerous because of the potential for multi-generational harm. Smoking is associated with poorer pregnancy outcomes including infertility, ectopic pregnancy, increased rates of spontaneous abortion and still births. Smoking contributes to preterm birth, low birth weight, increased rates of infant chronic lung disease, wheezing, and an increased risk for Sudden Infant Death Syndrome (DiFranza & Lew, 1996).

1.5 Epidemiology of tobacco smoking and related harm in the mental health population

1.5.1 Prevalence of smoking

Around 60-90% of people with schizophrenia are estimated to smoke, compared with 15-24% of the adult general population (Keltner & Grant, 2006; Ziedonis et al., 2008; Diaz et al., 2009; Kotov et al., 2010; Dickerson et al., 2013; Smith et al., 2014, Davies 2014). The difference of 30 percentage points from 60% to 90% is large and may reflect the geographic location of the study or a different classification system used for schizophrenia spectrum disorders diagnosis, for example DSM classification used by the American Psychiatric Association (APA) or International Classification of Diseases (ICD) classification used by the WHO.

Alternatively, the wide range in prevalence may be due to methodological differences between studies. As in the general population, in the study of de Leon & Diaz (2005), more males than females with schizophrenia were smokers (76% of males vs 50% of females).

The association between smoking and mental health conditions becomes stronger relative to the severity of the mental condition, with the highest levels of 70% smoking found in psychiatric in-patients (RCP, 2013; Jochelson et al., 2007). It was estimated in 2013 that of the ten million smokers in the UK about three million had a mental health condition (RCP, 2013).

DSM-V (APA, 2013) describes 157 specific diagnoses. It is therefore important not to view 'mental health conditions' as one group, just as one would not consider 'physical health' as one condition. It is true that there is a high level of smoking prevalence amongst individuals with mental health conditions but it varies according to the actual mental health conditions, e.g. schizophrenia, anxiety disorders, major depression, bipolar disorder (Caponnetto, 2014). Rates of cigarette smoking amongst adults in the United States and United Kingdom are two to four times higher in people with current mood, anxiety, and psychotic disorders than in those without mental illness (Lasser et al., 2000; Lawrence et al., 2009). Between 2004 and 2011, after controlling for risk factors such as income, education, and employment, current smoking rates dropped from 19.2% to 16.5% in US residents without mental illness but not in those with mental illness (Cook et al., 2014).

1.5.2 Smoking behaviour

A study with more than 9000 people with severe psychotic disorders found that these people had a higher risk of having ever smoked 100 cigarettes (odds ratio (OR) 4.61, 95% confidence interval (CI) 4.3 to 4.9) relative to the general population after controlling for sex, race, age, and geographical region (Hartz et al., 2014). Hughes et al. (1986) reported that people with chronic mental illness had substantially higher smoking rates than control samples across age, sex, marital, socioeconomic, and alcohol use subgroups, and the smoking rate was particularly high (88%) in patients with schizophrenia.

A meta-analysis of five studies across four countries established that tobacco smoking was associated with a schizophrenia diagnosis (OR = 5.9), heavier smoking (ORs ranged 1.9–6.4), higher nicotine dependence and lower cessation

rates compared with general population controls (de Leon & Diaz, 2005). Even patients with first-episode psychosis are much more likely to smoke than age-matched controls, as confirmed in a meta-analysis (OR = 6.04) (Myles et al., 2012).

In 2013, Zhang et al. enrolled 244 drug-naive smokers with schizophrenia and 256 healthy controls matched for gender, age and education, completed the Fagerström Test for Nicotine Dependence and showed that smokers with schizophrenia spectrum disorders are heavier smokers than those without a mental health condition (Zhang et al., 2013). However, it is important to outline that the study conducted by Zhang et al., (2013) included exclusively never-medicated participants presenting with first episode of schizophrenia.

In 2005, Tidey et al. enrolled 20 smokers with schizophrenia spectrum disorder and 20 smokers without psychiatric disorders and measured their smoking topography. The participants were matched on age, gender, daily cigarette rate, years of regular smoking and nicotine dependence. Tidey et al. (2005) reported that smokers with schizophrenia spectrum disorders take more frequent puffs and inhale more carbon monoxide (CO) per traditional cigarette and are highly dependent on nicotine compared with people in the general population. However, this study is limited by the small sample size. Smokers with schizophrenia spectrum disorders also extract more nicotine from their cigarettes compared with controls without schizophrenia spectrum disorders and have higher levels of nicotine in their blood after smoking one cigarette (Williams et al., 2010a).

However, this study was limited by a small sample size of 21 participants (11 with schizophrenia spectrum disorders and 10 without) who smoked 20-30 traditional CPD. A further study by Williams et al. (2011), using a larger sample, measured serum nicotine levels and ad libitum smoking behaviour for 24 + two hours using a topography device in 75 smokers with schizophrenia compared with 86 control smokers without mental illness. They reported that smokers with schizophrenia differed from smokers without schizophrenia in that they took more frequent puffs per traditional cigarettes smoked, which was associated with greater nicotine intake, and waited less time between puffs.

1.5.3 Effect of smoking on the mortality and physical health of people with schizophrenia spectrum disorders

As a result of high smoking rates, people with a mental health condition also have high mortality rates compared with the general population. Therefore, quitting smoking is particularly important for this group since smoking is the single largest contributor to their reduced life expectancy (Campion et al., 2014). The deleterious effects of smoking seem particularly pronounced and burdensome amongst people with schizophrenia (Brown et al., 2000; Kelly et al., 2011). Smokers with schizophrenia die early from diseases associated with smoking (15-20 years earlier than the general population) and this is often due to preventable smoking-related health conditions rather than suicide (Saha et al., 2007).

In the United States, results from a recent retrospective longitudinal national review of premature mortality amongst 1,138,853 adults with schizophrenia demonstrated excess deaths from lung cancer, cardiovascular and respiratory diseases (Olfson et al., 2015). It is important to note that the findings from this research showed an excess of deaths especially due to cardiovascular and respiratory disease for which traditional cigarette use is a fundamental risk factor (but not the only one, because the use of other substances, such as alcohol, was also involved). The authors highlight a number of limitations in their study without considering the side effects of some antipsychotics, such as Clozapine, on cardiovascular parameters.

In people with schizophrenia spectrum disorder, the risk of mortality is doubled (Heiberg et al., 2018). About 50% of deaths in patients with chronic mental illness are due to tobacco-related cancers, respiratory diseases, and cardiovascular conditions (Kelly et al., 2011; Callaghan et al., 2014). Callaghan et al. (2014) found in a large-scale follow-up study that tobacco-related conditions comprised approximately 53% (23.620/44.469) of total deaths in the schizophrenia cohort, 48% (6.004/12.564) in the bipolar cohort, and 50% (35.729/71.058) in the depression cohort. This included an increased risk of tobacco-related deaths from cancer (standardised mortality ratio (SMR) 1.30, 95% CI 1.3–1.4), cardiovascular disease (SMR 2.46, 95% CI 2.41–2.50) and respiratory diseases (SMR 2.45, 95% CI 2.41–2.48) (Callaghan et al., 2014). However, these data refer exclusively to

smokers who received in-patient treatment and cannot be generalized to other smokers treated as outpatients.

Moreover, people with schizophrenia who smoke have poorer health compared with people with schizophrenia who do not smoke (Aubin et al., 2012).

An increased rate of smoking amongst subjects with schizophrenia spectrum disorders contributes to multiple negative health effects compared with the general population (Beary et al., 2012).

Specifically, several studies have shown that people with schizophrenia spectrum disorders have a significantly higher prevalence of cancer (Sokal et al., 2004), respiratory diseases (Sokal et al., 2004; Carney et al., 2006; Batki et al., 2009; Partti et al., 2015), and CVDs (Sokal et al., 2004; Carney et al., 2006; Batki et al., 2009) compared with the general population (Sokal et al., 2004; Carney et al., 2006; Batki et al., 2009).

A recent study conducted by Partti et al. (2015), showed smokers with schizophrenia had a greater likelihood of suffering from comorbid COPD compared with the general population, reporting an OR of 4.23 (1.61, 11.10). Based on these findings, COPD is more common in smokers with schizophrenia spectrum disorders compared with the general population. Other studies have also shown an increased risk of death from cancer (Tran et al., 2009; Partti et al., 2015) and cardiovascular disease (Druss et al., 2001; Osborn et al., 2007; Lawrence et al., 2013) with an approximately 12-fold increased risk of cardiovascular death in smokers compared with non-smokers (Kelly et al., 2011).

1.5.4 Effect of smoking on the mental health of people with schizophrenia spectrum disorders

Amongst smokers with schizophrenia spectrum disorders, smoking is associated with depressive symptoms, increased hospitalizations, stress, poor treatment outcomes, low quality of life, and enhanced psychotic symptoms (Dixon et al., 2007).

The association between tobacco addiction and neurocognitive performance in smokers with schizophrenia spectrum disorders is unclear. Several studies have demonstrated that nicotine administration has a role in enhancing cognition in schizophrenia, particularly for the attention/vigilance domain (Harris et al., 2004;

Smith et al., 2005; Hahn et al., 2013). Furthermore, the studies assessed several cognitive tests with different outcomes but the majority failed to control for multiple comparisons on cognitive assessment and the brief duration of these studies have not confirmed the long-term benefits to attention/vigilance. Recently, evidence has demonstrated that smoking may have a detrimental effect on the working memory (Lee et al., 2015) and hippocampal volume (Schneider et al., 2014) of people with schizophrenia. A recent systematic review and meta-analysis of comparative studies conducted by Wang et al. (2019) explored cognitive functions in smokers and non-smokers with schizophrenia spectrum disorders and found that smokers with schizophrenia spectrum disorders had lower neurocognitive performance in cognitive tasks than non-smokers with schizophrenia spectrum disorders.

In a recent systematic review and meta-analysis, Huang et al. (2019) explored the effect of traditional cigarette smoking on different psychopathological positive and negative symptoms of schizophrenia. Their meta-analysis of 24 studies examined positive and negative symptoms scores as assessed by the Positive and Negative Syndrome Scale (PANSS) or the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) in 2322 smokers and 2319 non-smokers with schizophrenia spectrum disorders and showed that smokers had more severe positive symptoms than non-smokers (SMD = 0.33, 95% CI: 0.16 to 0.50, $P < 0.001$) but the same study did not find any significant difference between smokers and non-smokers for negative symptoms (SMD = 0.11, 95% CI: -0.06 to 0.28, $P = 0.21$). This systematic review and meta-analysis (Huang et al., 2019) also investigated extrapyramidal side effects of smokers and non-smokers with schizophrenia spectrum disorders and showed less severe extrapyramidal side effects in smokers than non-smokers (SMD = -0.20, 95% CI: -0.38 to -0.02, $P = 0.03$). The strength of this systematic review and meta-analysis is that it included a large number of studies; however, it is important to consider that different diagnostic scales (using different items and therefore producing different scores) were used.

In schizophrenia spectrum disorders, smoking traditional cigarettes is associated with increased psychopathological symptoms and increased hospitalizations (Ziedonis et al., 1994). Kobayashi et al. (2010) conducted a retrospective study with

460 discharged patients with schizophrenia spectrum disorders in Japan. Smoking status and hospital psychiatric readmissions were reviewed and it was observed that psychiatric hospital readmission rates were significantly higher in smokers with schizophrenia compared with smokers without schizophrenia (HR = 1.78). Participants were voluntarily admitted to psychiatric hospitals for the first time and findings cannot be generalized to other populations or people in different stages of this illness. Smoking is also associated with an increased need for higher psychiatric medication doses. Cigarette smoking increases the activity of the cytochrome P450 1A2 (CYP1A2) liver enzyme system, thus reducing the blood concentrations of many drugs (Sagud et al., 2009) and this process can also have an impact on antipsychotic medication. A recent meta-analysis conducted by Tsuda et al. (2014) found that two commonly used antipsychotics in the treatment of schizophrenia spectrum disorders, olanzapine and clozapine, should be increased by 30% and 50%, respectively, in smokers compared with non-smokers in order to obtain an equivalent olanzapine or clozapine blood levels.

It has been suggested that smoking could act as a trigger for mental ill-health (West & Jarvis, 2005). Two recent meta-analyses conducted respectively by Gurillo et al. (2015) and Hunter et al. (2018) showed that smokers of traditional cigarettes have an ~two-fold increased risk of developing schizophrenia spectrum disorders. Gurillo et al. (2015) included five studies and reported an increased risk of developing a schizophrenia spectrum disorder in smokers compared with non-smokers (RR = 2.18; 95% CI 1.23–3.85). Also, Hunter et al. (2018) included five studies and reported a similar result (RR = 1.99; 95% CI 1.10–3.61), but in conclusion, further studies are needed to explore the association between traditional cigarette smoking as a predictor of developing a schizophrenia spectrum disorder.

1.6 Schizophrenia spectrum disorders: symptomatology, diagnostic criteria, prognosis, aetiology and principal treatments

Mental health conditions comprise a broad range of psychological conditions, with varying symptoms, characterized by a combination of abnormal thoughts, emotions, behaviour and relationships with others (WHO, 2010). As mental conditions are often defined as much by the severity of their symptoms as by the occurrence of

specific symptoms, diagnosis frequently relies on an assessment of the impact of symptoms on functioning (RCP, 2013).

Schizophrenia spectrum disorders are a range of linked conditions sometimes extending to include singular symptoms and disorders as they relate to psychology; they also refer to patterns of behaviour that impact multiple life areas and create distress for the person suffering them. Schizophrenia spectrum disorders are a range of disorders with the same symptoms as schizophrenia. Some of these disorders are delusional disorder, schizoaffective disorder, schizophreniform disorder, schizotypal personality disorder, and schizoid personality disorder (APA, 2013).

Schizophrenia is one type of chronic and severe mental illness. It is a heterogeneous mental disorder characterized by disturbances in emotion, behaviour and thought (WHO, 2001). The National Institute of Mental Health (NIMH, 2016) describes this disorder as a chronic and severe mental illness affecting how someone thinks, feels, and behaves. People affected by schizophrenia experience some of the most challenging clinical signs and symptoms evidenced by any mental disorders.

A review of 41 studies by Tajima-Pozo and colleagues suggested that schizophrenia is associated with a particularly high burden to society as many affected individuals are unable to work, and a substantial proportion may need additional help from caregivers (Tajima-Pozo et al., 2015). Schizophrenia is a mental disorder characterized by reduced emotional expression, abnormal social behaviour and the inability to distinguish what is real from what isn't. Persons with schizophrenia might talk about hearing voices, experience hallucinations, and suffer delusions. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (APA, 2013), schizophrenia affects men slightly more than women and typically begins in late adolescence or early adulthood. A diagnosis of schizophrenia requires two or more DSM-V Criterion A symptoms to be present for at least one month. The symptoms must include a delusion, hallucination, or disorganized speech. Other clinical signs and symptoms might include grossly disorganized or catatonic behaviour and negative symptoms (APA, 2013). Additionally, there must

be a decrease in the individual's level of functioning and signs of the illness must persist for at least six months (APA, 2013).

The DSM-V diagnostic criteria for schizophrenia are:

- Two or more of the following symptoms for a significant portion of time for at least one month; at least one symptom should be either 1, 2, or 3:
 - (1) Delusions
 - (2) Hallucinations
 - (3) Disorganized speech
 - (4) Grossly abnormal psychomotor behavior (e.g., catatonia)
 - (5) Negative symptoms (i.e., restricted affect or avolition/asociality)
- Functioning in work, relationships, or self-care have declined since onset
- Signs of disturbance for at least six months; at least one month of symptoms above; or, if during a prodromal or residual phase, negative symptoms or two or more of the symptoms in attenuated form.

The DSM-V diagnostic criteria for delusional disorder are:

- An illness characterized by at least one month of delusions but no other psychotic symptoms.
- Delusions are false beliefs based on incorrect inference about external reality that persist despite the evidence to the contrary; these beliefs are not ordinarily accepted by other members of the person's culture or subculture.
- Delusions can be characterized as persecutory, referential, grandiose, erotomanic, nihilistic, or somatic.

The DSM-V diagnostic criteria for schizoaffective disorder are:

- Presence of a generally continuous psychotic illness plus intermittent mood episodes for at least one month.

- Mood episodes are present for the majority of the total duration of the illness, which can include either one or both of the following: Major depressive episode (must include depressed mood); Manic episode
- The psychotic illness criteria resemble Criterion A of the schizophrenia diagnosis

The DSM-V diagnostic criteria for schizophreniform disorder are characterized by the presence of the symptoms of schizophrenia, but it is distinguished from that condition by its shorter duration, which is at least one month but less than six months.

The DSM-V essential features of the schizotypal personality disorder are:

- Significant impairments in personality functioning manifest by:
 - Impairments in self functioning.
 - Impairments in interpersonal functioning.
- Pathological personality traits in the following domains:
 - Psychoticism.
 - Detachment.
 - Negative Affectivity.

The DSM-V essential features of the Schizoid personality disorder are:

- A persistent pattern of disinterest from social interactions and a limited variety of expression of emotions in a close personal setting as shown by at least four (or more) of the subsequent:
- neither wants nor likes close relationships, counting being part of a family
- almost constantly picks introverted activities
- has little if any, thought in engaging in any sexual experiences
- seldom derives pleasure from any activities
- has no close friends other than immediate relatives
- appears apathetic to the admiration or disapproval of others
- shows emotional coldness, detachment, or flattened affectivity

Symptoms can be distinguished by positive, negative, cognitive and disorganized symptoms (APA, 2013; NIMH, 2016). Positive symptoms include excesses and distortions, hallucinations, delusions, or thought disorders. Negative symptoms are associated with disruptions in normal emotions or behaviours, and include a flattened affect, avolition, alogia, anhedonia, and asociality reduced feelings of pleasure, difficulty beginning or sustaining activities, or reduced speech. Cognitive symptoms, which might be subtle or severe, include difficulties with executive functioning (i.e. planning and decision making), focus, attention, or memory. Disorganized symptoms include disorganized speech and disorganized behaviour (APA, 2013; NIMH, 2016).

Schizophrenia has a lifetime prevalence of approximately 0.5 to 1%, though schizophrenia spectrum disorders and subclinical traits likely affect a much broader segment of the population (Lenzenweger, 2006; Owen et al., 2016). Once a diagnosis is made, a person living with schizophrenia spectrum disorders will fluctuate between three distinct phases: the acute phase, stabilization, and the stable (or chronic) phase (APA, 2013). The acute phase may develop gradually or suddenly. Symptoms are often severe and individuals require professional help. During stabilization, treatment is initiated (or re-initiated) and there is a reduction in acute symptoms. Finally, in the stable phase, acute symptoms are managed, but some functional disability may persist (APA, 2013). Despite advances in the treatment of schizophrenia spectrum disorders, many patients continue to show persistent negative (Chue & Lalonde., 2014) and positive symptoms of schizophrenia (Suzuki et al., 2012).

It has been estimated that around two-thirds of patients still experience significant positive symptoms two years after initiation of antipsychotic treatment, and approximately 33% will continue to experience these symptoms six years after diagnosis of schizophrenia (Novick et al., 2009). Poorly controlled positive symptoms lead to poor patient outcomes such as relapse, rehospitalization, impaired functioning, and a reduced quality of life (Novick et al., 2009; Jordan et al., 2014). Many patients experience persistent negative symptoms even after control of positive symptoms (Chue and Lalonde, 2014). Severe negative symptoms

are a predictor of poor patient functioning and also contribute to worse patient outcomes (Jordan et al., 2014).

People with schizophrenia spectrum disorders with persistent symptoms represent a great challenge in their treatment management and, given the disorders' complexity, scientific literature shows a number of causal factors are likely to contribute.

The genetic evidence is strong, with much of the evidence coming from family, twin, and adoption studies. Learning what is inherited remains a challenge for molecular genetics studies (Walker et al., 2008). Linkage studies have found linkage on several chromosomes, but these studies need to be replicated.

Neurotransmitters play a role in schizophrenia spectrum disorders. For years, dopamine was the focus of study, but later findings led investigators to conclude that this one neurotransmitter could not fully account for schizophrenia. Other neurotransmitters are also the focus of study, such as serotonin, gamma-Aminobutyric acid (GABA), and glutamate (Volk et al., 2000; MacDonald et al., 2006). A number of different brain areas have been implicated in schizophrenia. One of the most widely replicated findings is of enlarged ventricles (Hajima et al., 2013). Other research supports the role of the prefrontal cortex, particularly reduced activation of this area, in people with schizophrenia spectrum disorders (Ohtani et al., 2014). Some of these structural abnormalities could result from maternal viral infection during the second trimester of pregnancy or from damage sustained during a difficult birth (Walker et al., 2004).

Early developmental studies looked back at the childhood records of adults with schizophrenia spectrum disorders and found that some adults with schizophrenia spectrum disorders had lower intelligence quotients (IQs) and were withdrawn and delinquent as children (Berry, 1967; Watt, 1974). Other studies found that adults who later developed schizophrenia spectrum disorders expressed a lot of negative emotion and had poor motor skills (Walker et al., 1993; Walker et al., 1994) and these studies have found that children at risk for adult schizophrenia spectrum

disorders have difficulties with attention and motor control, amongst other things (Woodberry et al., 2008).

During the acute phases of the illness, treatment of schizophrenia spectrum disorders most often includes a combination of short-term hospital stays, medication, and psychosocial treatment. Antipsychotic drugs have been widely used to treat schizophrenia since the 1950s. Second-generation antipsychotic drugs, such as clozapine, olanzapine and risperidone, are effective and produce fewer motoric side effects compared with first generation drugs, though they have their own set of side effects (McEvoy et al., 2014). Drugs alone are not a completely effective treatment, though, as people with schizophrenia spectrum disorders need to be re-taught ways of dealing with the challenges of everyday life (Kreyenbuhl et al., 2010).

Family psychotherapy aimed at reducing high levels of expressed emotion has been shown to be valuable in preventing relapse in people with schizophrenia spectrum disorders (Guo et al., 2010). Psychoeducation and social skills training have helped people with schizophrenia spectrum disorders meet the inevitable stresses of family and community living (Kopelowicz et al., 2002). Efforts to change the thinking of people with schizophrenia spectrum disorders by strategies emerging from cognitive behavioural therapy (CBT) are showing promise as well (Elis et al., 2013). In conclusion, the most promising approaches to treatment today emphasize the importance of both pharmacological and psychosocial interventions.

1.7 Theory explaining high smoking rates and high nicotine dependence in smokers with schizophrenia spectrum disorders

The reasons for the high frequency of both high nicotine dependence and high smoking prevalence in patients with schizophrenia spectrum disorders are incompletely understood. Explanations for the phenomenon of high rates of smoking are included in the next subsections. Illness-related factors, patient-related factors and health service-related factors have been considered in an attempt to find a reason for the relationship between high smoking rates and schizophrenia but have failed to arrive at decisive conclusions.

1.7.1 Illness-related factors

Studies have presented a number of illness-related reasons for high smoking rates and high nicotine dependence in smokers with schizophrenia spectrum disorders.

Nicotine evokes its physiological effects by binding with nicotine acetylcholine receptors (nAChRs) and strengthens rewards from brain stimulation. nAChRs also play an essential role in cognitive processes such as memory and learning (Yann et al., 2008) and researchers have shown abnormalities of nAChRs in people with schizophrenia (D'Souza & Markou, 2012; Parikh et al., 2014).

Schizophrenia is linked to elevated dopamine levels in dorsal striatum and reduced cortical dopamine release (Howes et al., 2017). Dopamine is a neurotransmitter system influenced by nAChRs (Albuquerque et al., 2009). All antipsychotic medications act on the dopaminergic system by blocking dopamine receptors of the D2-type family (Ellenbroek, 2012). Nicotine increases dopamine levels in the striatum by stimulating its release via nicotinic receptors and decreasing its degradation by inhibiting monoamine oxidase A and B. These produce a stimulation effect and a reduction of anti-psychotic extrapyramidal side effects (Sagud et al., 2009). It has been suggested that in people with schizophrenia spectrum disorders, traditional cigarette smoking is a way to self-medicate by reducing problems associated with antipsychotic treatment (e.g. extrapyramidal symptoms) and reducing positive and negative psychotic symptoms (Leonard & Adams, 2006), attempting to remediate cognitive performances as a result of the underlying schizophrenia spectrum disorders symptoms and stimulating attention and working memory (Sacco et al., 2005).

However, some aspects of the above theories are questionable. For example, if smoking traditional cigarettes reduces problems associated with antipsychotic treatment, tobacco consumption in smokers with schizophrenia should change with changes of antipsychotic drugs. Also, smokers and non-smokers with schizophrenia should show significant differences in their behaviours in terms of positive and negative symptoms phenomenology.

Kumari & Postma (2005) suggested the smoking rate in people with schizophrenia increased due to nicotine's improving effect on schizophrenia symptoms. Studies have described positive neurocognitive effects of nicotine in principal cognitive domains (attention, processing speed, working memory, and psychomotor abilities)

in individuals with cognitively impaired people with schizophrenia.

Research conducted by Barr et al. (2008a) examined the effect of transdermal nicotine (14 mg nicotine patches) and placebo in non-smoking individuals with schizophrenia (n=28) and healthy controls (n=32) in a within-subject study and showed that nicotine improved cognitive performance in both groups in terms of attention, but patients with schizophrenia showed greater improvement in inhibition and impulse control compared with healthy controls. In a second study, Jubelt et al. (2008) investigated the effect of transdermal nicotine on episodic memory performance in non-smoking individuals with (n=10) and without schizophrenia (n=12). Compared with placebo control conditions, both groups increased in processing speed and accuracy in recognising novel objects but there was a trend for a stronger nicotine-induced effect in schizophrenic patients in the reduction of false alarms and this is important considering that memory deficits are associated with functional impairment in schizophrenia and that impaired novelty detection has been linked to the positive symptoms of schizophrenia. However, it's important to consider that these findings refer to non-smokers with schizophrenia using nicotine not delivered by traditional cigarettes.

Further studies have assessed the impact of nicotine intake on cognitive function in people with schizophrenia spectrum disorders (D'Souza & Markou, 2012). Despite the differences in level of nicotine dependence, severity of nicotine withdrawal, craving and satiety and method of nicotine administration (gum, transdermal patch, nicotine nasal spray) amongst participants in several different research studies, findings suggest nicotine administration has a role to play in enhancing cognition in schizophrenia, particularly for attention/vigilance (Harris et al., 2004; Smith et al., 2005; Hahn et al., 2013). However, none of these studies has used cognitive psychodiagnostic tools specifically designed for people suffering from schizophrenia spectrum disorders, such as the Brief Assessment of Cognition in Schizophrenia (BACS) (Kefee et al., 2004), or MATRICS Consensus Cognitive Battery (MCCB) scales (Nuechterlein et al., 2008), but have instead used psychodiagnostic tools created for the general population such as the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998), Spatial Attentional Resource Allocation Task (SARAT) (Hahn et al., 2006), and Singleton Detection Task or Continuous Performance Task (CPT) (Conner, 2000).

A Spanish study (Aguilar et al., 2005) explored the association between frequency of smoking and severity of positive symptoms and number of hospitalisations amongst 250 outpatients with schizophrenia. Patients were classified into three categories: highly dependent smokers, mildly dependent smokers and non-smokers. High PANSS total scores and positive symptoms were less frequent in mildly dependent smokers than in non-smokers or highly dependent smokers. The highly dependent smokers had the worst outcomes. Aguilar et al. (2005) argued that their data did not support the self-medication hypothesis but rather suggested a complex interaction between nicotine dependence and symptoms of schizophrenia.

The self-medication theory has generated further criticism; for example Manzella et al. (2015) generated a list of predictions from the self-medication hypothesis applied to smoking traditional cigarettes in patients with schizophrenia spectrum disorders and concluded that further consideration of the neurophysiological data was needed to resolve the countering effects of nicotine-dopamine interactions on negative and positive symptoms of schizophrenia. Secondly, the evidence is contradictory that smokers with schizophrenia spectrum disorders have fewer signs and symptoms than non-smoking patients. Thirdly, there is no information whether smoking traditional cigarettes reduces undesirable side effects of antipsychotic pharmacological treatments while leaving unmodified the positive effects of these drugs. Environmental and genetic aspects play roles in the aetiology and progress of nicotine addiction and schizophrenia. Patients affected by schizophrenia have abnormal expression of certain genes which are common to nicotine addiction and schizophrenia disorder (Riley et al., 2000; Mexal et al., 2010; Purcell et al., 2014; Owen et al., 2016). However, this does not completely explain the high smoking rates in smokers with schizophrenia spectrum disorders.

1.7.2 Patient-related factors

Another possible explanation could be that smokers with schizophrenia spectrum disorders have a subjectively more rewarding experience when smoking compared with others. For example, Spring et al. (2003) studied the reward value of smoking traditional cigarettes (compared with other pleasant activities, e.g., eating their favourite candy, seeing a movie, receiving a gift) in individuals with schizophrenia

(n=26) as well as healthy controls (n=26). All participants were nicotine-dependent, heavy smokers who had smoked since their teenage years and there were no differences between groups in the number of cigarettes smoked per day at baseline (BL). Their findings showed that participants did not differ in their perception of negative consequences related to smoking traditional cigarettes. However, smokers with schizophrenia differed significantly from controls in their evaluation of positive smoking-related effects. Although they recognized smoking related disadvantages to the same extent as the general population, they perceived more benefits and found traditional cigarettes more appealing than alternative rewards, indicating that their higher smoking rates are mediated by reward-related experiences. However, this study only considered that traditional cigarette smoking, and not exclusively nicotine, had greater reward value for smokers with schizophrenia. Future research should differentiate between nicotine and cigarette smoking and its reinforcing effects associated with sensorial and behavioural impact on reward perception.

In 298 smokers with psychosis living in the community, Baker et al. (2007) reported that, compared with general population samples, patients with psychosis were more likely to indicate that addiction, stimulation and stress management were reasons for smoking traditional cigarettes. Dixon et al. (2007) examined the correlates and sequelae of smoking severity in 304 smokers with schizophrenia. Greater smoking severity was associated with poorer overall self-reported subjective quality of life, greater perceived stress, and lower satisfaction with relaxation activities, social relationships, finances and health amongst persons with schizophrenia. Greater smoking severity was also associated with greater perceived stress, poorer overall subjective quality of life, and lower satisfaction with finances, health, leisure activities, and social relationships (Dixon 2007). Some people with schizophrenia perceive that smoking traditional cigarettes helps to manage stress, whereas heavy smokers report increased stress levels.

A study of Esterberg & Compton conducted in 2005 used semi-structured interviews to explore reasons for smoking amongst 12 smokers (ages 19 to 43 years, median 25.5) with schizophrenia spectrum disorders. Their findings showed many reported perceived benefits associated with smoking traditional cigarettes, including that smoking traditional cigarettes was considered important to decrease anxiety, relieve

boredom and increase motivation and concentration. McCloughen et al. (2003) suggested that high smoking rates and high nicotine dependence in smokers with schizophrenia are explained by personal and social factors: many people with schizophrenia spectrum disorders are unemployed and inactive, and smoking was reported to relieve boredom and improve low self-esteem.

Kelly et al. (2012) examined the perceived consequences and benefits of cigarette smoking and motivation for quitting in 100 nontreatment-seeking smokers who had schizophrenia or schizoaffective disorder and 100 people without a psychiatric disorder. People with schizophrenia reported that cigarette smoking made socialising easier compared with the control group. They also had a lower appreciation for health risks associated with cigarette smoking than controls. Potential health consequences were found to be a less compelling reason to quit smoking compared with the control group.

1.7.3 Health service- and health professionals-related factors

Smoking cigarettes is frequently socially accepted amongst smokers with schizophrenia spectrum disorders (Trainor & Leavey, 2017; Twyman et al., 2014) and many smokers with schizophrenia spectrum are not given smoking cessation treatment from health professionals providers (Goldberg, 2010; Trainor et al., 2017). Two studies found that smokers with schizophrenia spectrum disorders were less likely to be advised to quit compared with smokers without schizophrenia spectrum disorders (Briskman et al., 2012; Duffy et al. 2012).

Brown et al. (2015) studied the perceptions of 49 mental health professionals in providing the “5 A's” (ask, advise, assess, assist, arrange) of smoking cessation to smokers with schizophrenia. Clinicians rated a perceived lack of interest amongst patients and the impact of delivering the intervention on staff time as the greatest barriers to smoking cessation in this population.

Health service and mental health professionals have an important role in encouraging quit attempts and can guide the application of smoking cessation treatment in clinical practice (Prochaska, 2011) but several mental health professionals believe stopping smoking traditional cigarettes may worsen their

patients' condition, and some mental health professionals feel that they are taking away one of their patients' only pleasures in life (Ratschen et al., 2009; Johnson et al., 2010); hence, health service- and health professionals-related barriers are other possible reasons for high smoking rates in people affected by schizophrenia spectrum disorders.

1.8 Motivation to quit smoking in the general population and motivation to quit smoking in people with schizophrenia spectrum disorders

Generally, motivation is theorised as willingness to change (Biener & Abrams, 1991) and plays a central role in the smoking cessation process (Baker et al., 2004). Past and recent studies show that motivation to quit is a key factor in successful quit rates (Biener & Abrams, 1991; Jardin & Carpenter, 2012).

In relapse prevention theory (Witkiewitz & Marlatt, 2004), motivation is an important element in quitting smoking and avoiding relapse.

One theory regarding motivation to quit is "PRIME" theory (West., 2009). This theory of motivation considers plans, responses, impulses, motives and evaluations as important factors in motivation to quit.

This theory suggests smokers' evaluative beliefs about smoking traditional cigarettes, internal impulses and external triggers, have an important impact on the decision about smoking cessation.

Another model used to explain motivation to quit smoking is the Transtheoretical Model (Prochaska & DiClemente, 1983), which assumes that a smoker goes through precontemplation, contemplation, preparation, action, and maintenance stages of behaviour, each having a different level of motivation, before quitting successfully.

Data from general population studies indicate that motivation to quit is strongly related to quit attempts but not to successful smoking cessation (West et al., 2001; Zhou et al., 2009). However, other studies have found that higher levels of motivation increase the likelihood of maintaining smoking cessation (Boardman et al., 2005; Heppner et al., 2011), implying that there are different opinions about how motivation to quit relates to successfully quitting smoking in the general population.

A recent study addressed how motivation to quit smoking, assessed prior to a quit attempt in a sample of treatment-seeking smokers, predicted short-term quit rates at four weeks and medium-term at six or 12 months abstinence and showed that BL motivation to quit was not important in determining the success of quit attempts (Ussher et al., 2016).

Studies on motivation to quit traditional cigarettes have been mainly undertaken with the general population and very few studies have focused on the motivation to quit in special populations such as patients affected by schizophrenia spectrum disorders. Siru et al. (2009) conducted a systematic review of motivation to quit in people with mental health disorders compared with the general population. Fourteen studies were identified and people with psychotic disorders were found to be less motivated to quit smoking than individuals with depression. Addington et al. (1997) showed, amongst a sample of 60 smokers with schizophrenia, that more than 50% of the sample were motivated to reduce or to quit smoking traditional cigarettes and showed the same reasons to reduce or to quit reported by the general population, principally health worries and social encouragement. Etter et al. (2004) evaluated the stages of change in 151 patients with schizophrenia spectrum disorders compared with 742 people in the general population. The level of motivation to quit was similar in both groups. Amongst current smokers, the distribution of stages of change was similar in patients with schizophrenia or schizoaffective disorder (precontemplation 79%, contemplation 18%, preparation 3%) and in the general population sample (74%, 22%, and 4%, $p = 0.6$).

As part of an RCT to test the efficacy of bupropion in 41 smokers with schizophrenia, Mann-Wrobel et al. (2011) assessed motivation and confidence to quit: 61.5% considered quitting in the next month and 85% in the following six months, with 70% motivated to quit forever. However, half of the participants reported low levels of confidence in quitting.

Therefore, even though there is evidence that motivation to quit in smokers with schizophrenia spectrum disorders is quite similar to those of smokers without mental illness, it is evident that it is more difficult to help them to quit (Streck et al., 2018).

Therefore, additional effective strategies of traditional cigarette smoking cessation, reduction and THR approach are needed.

1.9 Smoking cessation treatments in the general population

Offering help to quit tobacco use in people dependent on tobacco is one of the six proven policies identified by the WHO Framework Convention on Tobacco Control (FCTC) to address the tobacco epidemic (WHO 2003; UCDC, 2004). Key barriers to developing national smoking cessation policies and tobacco-control supportive programmes are: inadequate training and lack of motivation amongst healthcare providers to undertake and deliver smoking cessation activities; lack of resources and government funding; unavailability and inaccessibility of pharmacotherapy products; the absence of mechanisms for financing or subsidising pharmacotherapy products by insurance companies; lack of coordination between various sectors involved in providing smoking cessation interventions; and, more importantly, the lack of integration of smoking cessation interventions into an overall policy on tobacco control. The FCTC came into force on February 27, 2005 and requires Parties to implement evidence-based measures to reduce tobacco use and exposure to tobacco smoke (WHO, 2013).

Article 14 of the FCTC requires Parties to take effective measures to promote cessation and adequately treat tobacco dependence. Guidelines for the implementation of Article 14 recommend establishing specialized tobacco dependence treatment services, making medications widely available and considering emerging research evidence and novel approaches to cessation.

The 2008 US Guide to Quitting Smoking recommends that, except for groups with contraindications or for whom smoking cessation drugs have uncertain efficacy (e.g., users of smokeless tobacco, light smokers, pregnant women, nursing women, and teenagers), clinicians should encourage all smokers intending to quit smoking to take smoking cessation medications combined with smoking cessation advice (Fiore et al., 2008).

There is evidence regarding the efficacy of the drugs used in smoking cessation (Bauld et al., 2010; Cahill et al., 2013). The drugs are most effective when used in

combination with behavioural therapies and support. Cognitive and behavioural interventions, such as motivational interviewing and relapse prevention, are an essential adjunct for the efficacy of these treatments (Bauld et al., 2010; Cahill et al., 2013).

In the general population there are three principal approved drug therapies, according to US International Guidelines: Nicotine replacement therapy (NRT), varenicline, and bupropion (Fiore et al., 2008).

Nicotine replacement therapy. NRT has an established evidence base in the general population. Multiple formulations are available – gum, lozenges, oral strips, sublingual tablets, inhalers, mouth and nasal sprays, and transdermal patches (16- or 24-hour release). All have comparable efficacy. These different formulations allow for better tailoring to individual requirements including the use of combinations if required. For example, a patient may be prescribed a transdermal nicotine patch and additionally use a nicotine inhaler to supplement blood nicotine concentrations at times of particular craving or risk of relapse (Stead et al., 2012). The OR of abstinence for any form of NRT compared with placebo is 1.84 (Cahil et al., 2013). Combined NRT formulations have been shown to result in higher abstinence rates than single NRT. The OR of abstinence for combination NRT compared with single NRT products is 1.43 (Cahil et al., 2013).

Varenicline. Varenicline has comparable efficacy with combination NRT but has superior efficacy to nicotine replacement monotherapy. It is therefore recommended as an equal first-line drug for smoking cessation. Varenicline acts as a partial agonist at central nicotinic acetylcholinergic receptors, which are important in mediating the reinforcement associated with tobacco smoking. During treatment, drug binding partially activates these receptors thereby reducing withdrawal symptoms and cravings. If the patient lapses and smokes, varenicline reduces the access of nicotine to the receptors. By limiting nicotine binding, varenicline reduces its rewarding effect. It is recommended that varenicline is started a week or two before the patient quits smoking. This is because a continuous period of dosing is required before sufficient receptors are occupied and optimal drug efficacy is achieved. The recommended dosage is one mg twice daily (for 12 weeks) following a one week

up-titration (Fiore et al., 2008). In the most recent Cochrane review, Cahill et al. (2016) reported that the OR of continuous abstinence for varenicline compared with placebo was 2.24; varenicline was more effective when compared with bupropion (OR 1.39) and single-product NRT (OR 1.25), and was similarly effective compared with combination NRT. Varenicline is principally eliminated by the kidneys so reduced doses (or alternative treatments) are recommended for patients with renal impairment. Common adverse effects include nausea, headache and insomnia.

Bupropion. Bupropion was originally developed as an antidepressant. It has dopaminergic and adrenergic actions and is an antagonist at the nicotinic acetylcholinergic receptor; however, its precise mode of action in smoking cessation is uncertain. It has equivalent efficacy to nicotine replacement monotherapy but is less effective than varenicline and is therefore considered a second-line option (Fiore et al., 2008). The recommended dosage of bupropion is 150 mg twice daily. Several meta-analyses have confirmed the efficacy of bupropion (Hughes et al., 2007; Fiore et al., 2008). In a network meta-analysis by Cahill et al. (2013), the OR of abstinence for bupropion compared with placebo was 1.82. Bupropion was of similar efficacy to single product NRT (RR 0.99) and less effective for quitting compared with varenicline and combination NRT. Bupropion has been shown to decrease nicotine/tobacco withdrawal symptoms and cigarette cravings (Mooney & Sofuoglu, 2006). Bupropion is contraindicated in patients with a history of seizures. Common adverse effects include difficulty concentrating, insomnia and nightmares. Bupropion undergoes significant hepatic CYP 2B6 metabolism to an active metabolite (hydroxybupropion), which is later excreted renally. Dose reduction is necessary in patients with hepatic or renal disease. There are potential interactions with other drugs metabolized by this system including antipsychotics and selective serotonin reuptake inhibitors.

1.10 Smoking cessation treatments for people with schizophrenia spectrum disorders

PubMed (National Library of Medicine), and PsycINFO (Ovid) were searched with the assistance of a trained librarian experienced in developing search strategies for reviews. Concepts that made up the search were: smoking cessation and schizophrenia. The search was not restricted by language or geographical region,

and was carried out by combining an exhaustive list of terms denoting schizophrenic disorder (schizophrenia or psychotic or psychosis or severe mental illness) AND smoking cessation treatment (smoking cessation treatment or varenicline or tobacco cessation or reduction or bupropion or NRT or behavioural treatment). Additionally, reference lists of all included papers were checked for any citations missed by electronic database searching. Cohort and case-control study designs were considered eligible for inclusion.

Cross-sectional studies, case series and case reports were included. The publication dates were limited to January 2006 to February 2018. Relevant articles were also searched in Scopus (Elsevier) to determine if they were cited by studies that previous searches had not found. We identified 77 original studies from the electronic search of the databases (39 studies from PubMed and 38 from PsycINFO).

These studies found evidence suggesting that pharmacotherapy for smoking cessation is effective amongst smokers with schizophrenia spectrum disorders, although more long-term research is required.

Actual licensed aids to smoking cessation in smokers with schizophrenia spectrum disorders still yield low long-term abstinence rates (Cather et al., 2017) and a meta-analytic study showed that for randomised controlled studies using bupropion or bupropion combined with NRT, the odds of smoking abstinence at six months were less than one in five participants (Tsoi et al., 2013).

Nicotine replacement therapy

Seven studies evaluated NRT for smoking cessation in smokers with schizophrenia spectrum disorders.

Four observational studies of open label NRT plus psychosocial treatment with motivational interviewing and CBT components have been conducted in smokers with schizophrenia. Three studies in 24-65 outpatients found quit rates of 9-14% at six-month follow-up assessments (Ziedonis et al., 1997; Addington et al., 1998; George et al., 2000) and one study in 68 outpatients found a 23% continuous abstinence rate at three-month follow-up (Chou et al., 2004).

In the largest smoking study in this population, 298 outpatients with a psychotic disorder (57% with schizophrenia) were randomised to routine care or to 10 weeks of treatment with motivational interviewing and CBT plus NRT (Baker et al., 2006). At the 12 month follow-up assessment, abstinence was not significantly higher in the treatment group (10.9%) compared with the control group (6.6%) (OR 1.72, 99% CI 0.58 to 5.09), but significantly more people in the treatment group had reduced the number of cigarettes they smoked each day by half (2.09, 99% CI 1.03 to 4.27). In addition, authors affirmed that the study groups showed significant improvement as a whole on several mental health questionnaires and absence of exacerbations of psychotic symptoms, but they used mental health questionnaires not specifically validated for schizophrenia spectrum disorders.

One placebo-controlled study investigated the efficacy of NRT for the prevention of relapse in smokers with schizophrenia (Horst et al., 2005). Fifty outpatients received nicotine patches that delivered 14-42 mg per day for 90 days along with weekly group motivational support. Those who quit (36%) were then randomised to continue receiving nicotine patches (same dose) or to receive placebo patches, along with biweekly group support, for another six months. At the end of this period, significantly more people receiving NRT remained abstinent compared with those receiving placebo (67% v 0%; $P < 0.01$). However, the use of a high-level nicotine patch at 42 mg, although it can guarantee high levels of efficacy, makes the symptoms of nicotine overdose highly probable in cases where the subject continues to smoke.

In a Cochrane review that included 11 NRT studies, Tsoi et al. (2013) concluded that there is currently little evidence to support the effectiveness of NRT in people with schizophrenia despite the benefits in the general population.

Bupropion

Eight studies evaluated bupropion for smoking cessation in smokers with schizophrenia spectrum disorders.

Two placebo-controlled trials in 32 and 57 smokers with schizophrenia found that bupropion significantly increased continuous abstinence during treatment ($P <$

0.05), although these effects were not maintained at the three to six-month follow-ups (George et al., 2002; Evins et al., 2005). Two trials that compared bupropion plus NRT with placebo plus NRT in smokers with schizophrenia found that bupropion plus NRT significantly increased the odds of continuous abstinence during treatment but not at the three to 12 month follow-ups (D'Souza et al., 2012; Esterlis et al., 2013).

In an observational study that examined the efficacy of extended open label bupropion plus NRT, 41 smokers with schizophrenia received bupropion plus NRT (patch plus gum or lozenge) and CBT for three months. At the end of this period, those who were abstinent (42%) entered a 12 month relapse prevention phase with bupropion plus NRT and CBT (Cather et al., 2013). At the 12 month assessment, 59% had achieved four weeks of continuous abstinence. However, the four previous trials and the observational study based their conclusions on studies that used small sample sizes.

A Cochrane review by Tsoi et al. (2013) found that bupropion was associated with a three-fold increase in cessation in smokers with schizophrenia (risk ratio 3.03, 1.69 to 5.42 at end of treatment; 2.78, 1.02 to 7.58 at six months). In a recent systematic review and meta-analysis conducted by Peckham et al. (2017), eight trials comparing bupropion with placebo were pooled showing that bupropion improved quit rates significantly in the medium and long term but not the short term (short term RR = 6.42 95% CI 0.82–50.07; medium term RR = 2.93 95% CI 1.61–5.34; long term RR = 3.04 95% CI 1.10–8.42).

In the Evaluating Adverse Events in a Global Smoking Cessation (EAGLES) study (Anthenelli et al., 2016), the largest comparative study of licensed smoking cessation aids, 8,144 smokers of traditional cigarettes with or without a diagnosis of psychiatric disorder used three months of treatment or placebo with a further three months follow-up of non-treatment, showing that bupropion has superior continuous abstinence rates vs. placebo at weeks 9-12 and 9-24 in both cohorts. 4,116 smokers were in the psychiatric cohort and 9.5% were affected by schizophrenia spectrum disorders. However, the continuous success rates at week 12 and week 24 were larger for people without diagnosis of psychiatric disorders (week 12, 26.1%, week

24, 18.8%) compared with participants with psychiatric disorders (week 12, 22.6%, week 24, 16.2%) and success rates were not stratified according to the specific psychiatric diagnosis.

Varenicline

Seven studies evaluated varenicline for smoking cessation in smokers with schizophrenia spectrum disorders.

A placebo-controlled trial (n = 9) found that three in four smokers with schizophrenia taking varenicline achieved continuous abstinence during the last four weeks of the treatment period compared with no patients taking placebo (P = 0.14) and no increases were seen in psychiatric symptoms or suicidal ideation (Weiner et al., 2011). However, this research enrolled only nine participants, of which eight completed the study, and specific validated questionnaires for schizophrenia spectrum disorders, such as SAPS, SANS or PANSS, were not used to assess changes in schizophrenia symptoms. A multi-site placebo-controlled trial of varenicline with brief counseling in 128 smokers with schizophrenia found that varenicline significantly increased point prevalence abstinence at the end of treatment (19% v 4.7%; P < 0.05) but not at the six month follow-up (Barr et al., 2008b). However, it is important to clarify that these patients undertook 12 weeks of treatment with varenicline and an extension of the use of varenicline up to 24 weeks would have probably reduced relapse rates at six month follow-up. In the study of Barr et al. (2008b), rates of adverse events (AEs) were similar across conditions, and schizophrenia symptoms, assessed by SAPS and SANS scales, were stable or decreased in both groups.

Finally, a 10-site placebo-controlled trial investigated whether varenicline reduces smoking relapse (Evins et al., 2014). In total, 247 patients with schizophrenia spectrum or bipolar disorder were enrolled and 203, of which 185 (91%) with schizophrenia spectrum disorders, entered the open label treatment phase. Of these, 87 (43%) attained two weeks of continuous abstinence and entered the relapse prevention phase, in which they were randomised to varenicline or placebo with CBT. At week 52, point prevalence abstinence rates were significantly higher in people taking varenicline (60% vs. 19%; OR 6.2, 95% CI 2.2 to 19.2), and rates

of continuous abstinence from week 12 to 76 were also higher (30% vs. 11%; 3.4, 1.02 to 13.6).

Varenicline had no effect on psychiatric symptoms. Two patients in each group reported suicidal ideation during the maintenance phase but there were no suicide attempts. Thus, amongst smokers with schizophrenia who attained abstinence, varenicline was well tolerated and increased prolonged abstinence for as long as 76 weeks (Evins et al., 2014). However as declared by the authors, smokers were enrolled from community mental health centers so that the findings should be generalizable to the large majority of patients with schizophrenia spectrum or bipolar disorders who are cured in this kind of setting.

The EAGLES study showed that varenicline has superior continuous abstinence rates vs. bupropion, NRT patch and placebo at weeks 9-12 and 9-24 in smokers with and without a history of psychiatric disorders with no significantly increased neuropsychiatric safety risk vs. placebo (Anthenelli et al., 2016). However, the continuous success rates at week 12 and week 24 were larger for people without diagnosis of psychiatric disorders (week 12, 38%; week 24, 25.5%) compared with participants with psychiatric disorders (week 12, 33.5%; week 24, 21.8%) and success rates were not stratified according to the specific psychiatric diagnosis.

The Cochrane review by Tsoi et al. (2013), found that varenicline is associated with an almost five-fold increase in cessation (4.74, 1.34 to 16.71 at end of treatment). In the review and meta-analysis by Peckham et al. (2017), five trials comparing varenicline with placebo showed that the addition of varenicline improved quit rates significantly in the medium term (RR = 4.13, 95% CI 1.36–12.53). A network meta-analysis about the effectiveness and tolerability of adjunctive pharmacotherapy for smoking cessation in adults with serious mental illness (Roberts et al., 2016) suggests that varenicline and bupropion are effective and tolerable for smoking cessation in adults with serious mental illnesses. A review by Kishi and Iwata (2015) pooled five RCTs and found that varenicline performed no better than placebo in achieving smoking cessation (RR 0.79, 95% CI 0.58–1.08, n = 332); however, these authors combined findings of studies where participants were recruited into studies to test varenicline for health outcomes other than smoking cessation/reduction.

Behavioural interventions

Bennett et al. (2013) identified 11 studies investigating behavioural therapies in people with schizophrenia and found that in the short term these had good post-treatment abstinence rates of up to 42%.

In addition, Bennett et al. (2013) found that these interventions were well tolerated by people with schizophrenia and found no evidence of deleterious impact on psychiatric symptoms.

A study of 87 people compared higher versus lower intensity behavioural treatment delivered by trained mental health clinicians -- Treatment of Addiction to Nicotine in Schizophrenia (TANS) or Medication Management (MM) -- in smokers with schizophrenia who received NRT for 16 weeks and found no difference on abstinence (Williams et al., 2010b). TANS was a high intensity treatment of 24 sessions (45 minutes) delivered over 26 weeks and MM was a moderate intensity treatment of nine sessions (20 minutes) delivered over 26 weeks that combined with NRT treatment significantly reduced smoking consumption in smokers with schizophrenia spectrum disorders. This study showed that mental health professionals can be trained to help smokers with schizophrenia spectrum disorders to maintain traditional cigarette abstinence.

Considering all these aspects, it is important to also investigate harm reduction approaches for smokers with schizophrenia spectrum disorders.

Experiences of smoking cessation

A study conducted by Tulloch and collaborators (2016) explored quitting experience and concerns of 732 smokers, 430 with psychiatric illness (18 with schizophrenia spectrum disorders), in comparison with 302 without psychiatric illness. Participants, enrolled between June 2010 and March 2013 to participate in the FLEX (Flexible and Extended Dosing of NRT and Varenicline in Comparison to Fixed-Dose NRT for Smoking Cessation) trial, completed questionnaires assessing previously used cessation aids and concerns about their upcoming quit attempt. Smokers with schizophrenia spectrum disorders experienced distress and negative affect as the most common predictors of smoking relapse. The quit methods used by smokers with schizophrenia spectrum disorders were transdermal NRT (72.2%),

followed by NRT gum (11,1%), NRT lozenge (11,1%), NRT inhaler (11,1%), varenicline (11,1%) and bupropion (11.1%) compared with the following quit methods used by smokers without psychiatric illness: transdermal NRT (69.9%), followed by bupropion (43.6%), NRT gum (32,9%), varenicline (19,3%), NRT inhaler (12,9%), and NRT lozenge (8,2%).

Rae et al. (2015) interviewed 16 participants with serious mental illness (six with schizophrenia spectrum disorders) who had participated in a clinical trial comparing two smoking cessation interventions, the first using NRT alone and the second using NRT, motivational interviewing and a peer support group. Findings from semi-structured interviews suggest smoking cessation experiences were influenced by positive experiences of NRT, though access to e-cigarettes or medications available in pill form (e.g., varenicline and bupropion) were considered more effective and easier to use. The intervention itself (such as the presence of smoking cessation aids and group support), Individual factors, (such as mental health, physical health, and substance use), and social-environmental factors (such as difficult life events and social relationships) influenced whether someone quit or not. The authors acknowledged several limitations in their study such as the small sample size, all participants coming from the same smoking cessation intervention, the researcher not being blind to the smoking cessation status of participants during the data collection and analysis, the interpretative nature of the results and the fact that the data were self-reported by participants and consequently subject to the effects of recall and social desirability, and the use of the seven-day period of abstinence and not continuous smoking abstinence criterion to differentiate quitters from smokers. Also, the authors did not differentiate the findings on the basis of the distribution of the mental pathology enrolled in the study (schizophrenia/schizoaffective disorder (n = 6, 38%), depression (n = 5, 31%), bipolar disorder (n = 4, 25%), and anxiety disorder (n = 1, 6%) and the thematic analysis did not give clear percentages of responses but used vague terms such as 'many' and 'some'.

Knowles et al. (2016) qualitatively explored the experiences of a small sample of 13 participants with serious mental illnesses, of which eight had schizophrenia spectrum disorders, who used a 'bespoke smoking cessation' intervention, compared with their experience of standard smoking cessation services. The

authors, without specifying if participants were in a stable or unstable phase of their illness and without differentiating the findings on the basis of diagnosis, enrolled five people with bipolar disorder and eight with schizophrenia spectrum disorders). They found that this intervention was perceived positively because the bespoke intervention was more flexible and tailored compared with the previous standard smoking cessation programme.

In addition to the medication used, tailoring the smoking cessation support to the individual needs of the smoker affected by schizophrenia spectrum disorders may result in better outcomes.

1.11 Summary and conclusion

This introductory chapter included literature about the epidemiology of tobacco smoking in people with schizophrenia spectrum disorders, examined the relationship between smoking and mental health and showed a higher prevalence, frequency and impact of both high nicotine dependence and its harmful effects in patients with schizophrenia spectrum disorders compared with the general population.

People with schizophrenia spectrum disorders die on average earlier than the general population. Despite several existent theories, the reasons for high smoking rates are not fully understood. This chapter highlights the importance of increasing treatment options for this group of smokers, who find quitting difficult and have lower quit rates than the general population. Their high dependence on nicotine and severity of nicotine withdrawal symptoms suggest that a harm reduction approach may be more achievable and acceptable, particularly if this leads to eventual abstinence (McChargue et al., 2002; Hughes et al., 2006). E-cigarettes offer smokers with schizophrenia spectrum disorders an alternative to more well-established approaches to smoking cessation or reduction. The next chapter provides a literature review of e-cigarettes and their potential for helping this group of smokers reduce their harm from tobacco smoking.

CHAPTER 2: INTRODUCTION TO E-CIGARETTES

This chapter reviews key current literature on electronic cigarettes (e-cigarettes) to provide further background to the remainder of the thesis. It begins (Section 2.1) by describing the concepts of THR, which provides a framework for understanding e-cigarette use as an alternative or addition to more well-established approaches to smoking cessation described in Chapter 1. The chapter then describes (Section 2.2) e-cigarettes as a product category, their development and key characteristics. This includes an introduction to the e-cigarette used in the primary research later in the thesis (JUUL). Section 2.3 of the chapter then describes and critically assesses available studies and reviews of e-cigarettes for smoking cessation in the general population. Section 2.4 outlines the available (and very sparse) literature on e-cigarettes for smoking cessation in people with schizophrenia spectrum disorders and explains how the research conducted as part of the thesis contributes to addressing important research gaps.

2.1 Tobacco harm reduction

The history of THR may be traced back to at least 1974, with the publication of a special article in the *Lancet* by British tobacco addiction research expert Michael A.H. Russell (1974). In essence, harm reduction as part of a tobacco control strategy involves trying to separate the risk associated with inhaling smoke from that of taking nicotine. As Russell noted 30 years ago, "There is little doubt that if it were not for the nicotine...people would be little more inclined to smoke than they are to blow bubbles or light sparklers" (Russell, 1974).

More recently, the National Institute for Health and Care Excellence (NICE) in the UK has described THR as reducing the diseases and deaths caused by smoking traditional cigarettes (NICE, 2011). NICE produced the world's first formal guidelines on THR between 2011 and 2013. These guidelines address reducing harm from smoking traditional cigarettes in order to help smokers, particularly those who are highly dependent on nicotine, and may not be able (or do not want) to stop smoking in one step; may want to stop smoking, without necessarily giving up nicotine; and may not be ready to stop smoking, but want to reduce the amount that they smoke

(NICE, 2013).

Despite the NICE harm reduction guidelines, approved smoking cessation treatment in the UK and other countries normally requires nicotine addicted smokers to abstain from tobacco and nicotine entirely. Many smokers are unable – or at least unwilling – to achieve this goal, and so they continue smoking in the face of impending adverse health consequences. In effect, established approaches to smoking cessation present smokers with just two alternatives: stop smoking or suffer the harmful effects of continuing smoking. However, THR arguably provides a third choice for smokers. It involves the use of alternative sources of nicotine as a replacement for smoking. E-cigarettes as a product category can fit within a THR paradigm.

They can deliver nicotine without the combustion products that are responsible for nearly all of smoking's damaging effects. These products and key available evidence about their use is outlined in the next sections of this chapter.

2.2 E-cigarettes

E-cigarettes are a part of a series of emerging products often referred to as Alternative Nicotine Delivery Systems (ANDS) or Electronic Nicotine Delivery Systems (ENDS). The term ENDS was created by the WHO's Study Group on Tobacco Regulation in 2009 to classify a collection of battery-powered devices that provide nicotine flavourings and other additives to the user in aerosol form.

A first version of an e-cigarette was patented as early as 1965 in the USA by Gilbert (Gilbert 1965). The Gilbert e-cigarette resembled a traditional cigarette but instead of burnt tobacco, it allowed the user to draw warm flavoured vapour into the mouth or lungs. A cartridge held a chemical solution and an insulated tube or light bulb powered by a battery provided a heating element to heat the solution. However, despite this innovative idea, Gilbert was never able to bring this product successfully to market.

Some years later, in 1986, the 'Favor' cigarette was developed as a non-combustible nicotine-containing product that also resembled a cigarette in appearance (Ling and Glantz, 2005). The device was made of a plastic tube

containing a paper soaked with nicotine in order to simulate the traditional cigarette effect without vapour creation. The Food and Drug Administration (FDA) in the USA deemed this type of device to be a nicotine delivery system and as consequence classified Favor as a drug and banned it (Sleight, 2016).

Following these very early designs, the modern e-cigarette was developed in 2003 by a Chinese pharmacist, Hon Lik. He created an electronic atomizing cigarette for smoking cessation after his father (a smoker) died of lung cancer. This e-cigarette was composed of a battery-operated device designed to vaporize a liquid solution of propylene glycol and vegetable glycerine in which nicotine was dissolved. No tobacco was used in the device. Puffing activated a battery-operated heating element in the atomizer and the liquid in the cartridge was vaporized as a plume of a dense mist and inhaled (Hon 2003). This e-cigarette prototype showed promise, and as a result in 2004 it was introduced on the Chinese market under the company name Ruyan. From there many other companies began to develop similar devices building on this initial prototype. The technology and range of products rapidly evolved and the market grew considerably from 2010 onwards. These products have now spread rapidly across Europe, the USA and a number of other areas and countries (Sanford and Goebel, 2014).

2.2.1 E-cigarette market and types

As of 2014, it was estimated that over 460 e-cigarette brands were available on the global market (Zhu et al., 2014). However, despite the potential product differences, some characteristics of e-cigarettes appear to be consistent across products. These include: a cartridge containing propylene glycol or glycerine mixed with different nicotine concentrations and a battery powered heating component which transforms the liquid substance into an aerosol form when air is drawn through the device (Cobb et al., 2010). E-cigarettes are also sold as either disposable or reusable, refillable products. E-cigarette devices vary from first generation, second generation, and third and fourth generation products.

First-generation e-cigarettes appear similar to traditional cigarettes, usually with a white body made of plastic and a tan mouthpiece (other first-generation e-cigarettes were slightly longer or narrower than a traditional cigarette and were black or

coloured). These devices are described as “cigalikes.” First generation models included a cartridge designed for the part of the device that holds the e-liquid, which is either prefilled with the liquid or ready to be filled (Figure 1). The user then connects the cartridge to the heating element and atomizer that are themselves connected to the battery, and the “cigalike” is ready for use (Zhu et al., 2014).

Second-generation e-cigarettes include devices that resemble fountain pens, are large and cylindrical, and are often described as e-cigarettes with “tank systems” in consideration of the transparent reservoir that holds larger amounts of e-liquid (about two or three ml) than previous first generation “cigalike” models (Figure 1).

Third generation devices are a diverse product category, and they appear totally different from traditional cigarettes in their appearance, principally because many are square or rectangular and customizable by changing batteries and atomizers (Figure 1). Since the beginning of the availability of e-cigarettes’ component elements, users have been modifying their own e-cigarettes by building their own customized e-cigarettes, which are called “mods.” Users can adjust the battery voltage and combine the e-liquid, choosing different flavours and nicotine levels (Richtel., 2014; Lee & Kim., 2015).

Fourth generation devices are the most advanced and powerful and differ from third-generation e-cigarettes in the following small details: they enable control over the temperature of the heating coil and can be used at much higher power levels (e.g., >200 W) compared with most earlier e-cigarettes (Strongin, 2019).

Figure 1. Evolution in e-cigarettes models



2.2.2 The JUUL e-cigarette

E-cigarette devices have evolved substantially over time, from early-generation cigalike e-cigarettes to more advanced modifiable tank-style versions. One of the latest products to be introduced on the market, initially in the USA, is the JUUL e-cigarette (Truth Initiative, 2018). JUUL is a non-modifiable compacted closed system e-cigarette and represents one of a newer generation of pod devices (Figure 2).

Figure 2. JUUL e-cigarette



JUUL has two basic components: the device, which includes the battery and temperature regulation system, and the prefilled e-liquid cartridge, called a 'pod', that comes in a variety of flavours (tobacco, mango, mint, and others). The original JUUL device pods contained 0.7 mL of e-liquid with 5% nicotine by weight, although lower strength nicotine options are now on the market, particularly in Europe.

The JUUL pods also serve as the mouthpiece for the product. JUUL is rechargeable by a USB port and is rectangular and small in size, fashioned to look like a computer flash drive (Kee, 2018).

The characteristics that make JUUL different from its predecessors include its design (called the 'iPhone of e-cigarettes') (Radding., 2015), its high levels of nicotine (0.7 mL or 59 mg/mL per pod) and the use of a specific e-liquid formula, JUUL salts, based on the nicotine salts found in leaf-based tobacco rather than free-based nicotine. JUUL provides a nicotine concentration comparable with a traditional cigarette, with the nicotine peaking in about five min., and delivers nicotine 1.25–2.7 times faster than competing e-cigarettes on the market (Brown & Xing, 2015; Lawler, 2018; Juulvapor, 2018).

2.2.3 Existing evidence on e-cigarette harms and benefits

Although e-cigarettes have only become widely used in the last few years, research evidence on these devices has been growing rapidly. This evidence is not always consistent and sometimes contradictory, but there is a growing consensus that these products are significantly less harmful than traditional cigarettes (Farsalinos & Polosa 2014; Nutt et al., 2016). That said, important research questions remain regarding any potential harms from use and also the potential benefits of use.

These questions include, for example, whether these products are effective aids for smoking cessation, promote uptake by nontobacco users, sustain nicotine dependency via dual use, slow intentions to quit in dual users, or encourage relapse to cigarette use amongst former smokers (Glasser et al., 2017).

E-cigarette use is a complex and dynamically evolving behaviour. To advance knowledge of the impact of e-cigarettes use on smoking status, it will be necessary to conduct prospective studies considering relevant descriptors of vaping behaviour such as frequency of use (e.g. focusing on daily users, and not just on those who are experimenting), reasons for using e-cigarettes (e.g. to quit smoking vs. out of curiosity), and product design (e.g. closed vs. open systems, nicotine containing vs. non-nicotine containing products, etc.). Reasons for vaping, the type of device and e-liquid, frequency of use, and the accompanying sensory and craving-control experiences may have some impact on smoking behaviours (Polosa et al., 2017).

E-cigarettes have ingredients that are not inert and are likely to have some potential health risks. While traditional cigarette combustion generates toxic substances correlated with cancers, respiratory disorders and CVDs, e-cigarette usage delivers potentially toxic substances involving fine particulate matter, metals that are known to probably determine adverse health effects related to cancers, respiratory disorders and CVDs.

2.2.3.1 Recent studies on relative risks in comparison with smoking

E-cigarette-related toxicants and carcinogens: A number of studies have tried to assess the RRs of e-cigarette use compared with tobacco smoking, in particular, the extent to which there is any reduction in exposure to harmful toxicants as compared with smoking traditional cigarettes.

For example, in one study, a research group provided 40 smokers with e-cigarettes in a choice of eight flavours with 12 mg or 24 mg of nicotine. The researchers collected urinary cotinine, the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), and eight volatile organic compounds at BL visit and a four week follow-up visit. They observed that CO ($p < .001$), NNAL ($p < .01$), and metabolites of benzene ($p < .01$) and acrylonitrile ($p = .001$) decreased significantly in smokers who switched to e-cigarettes (Pulvers et al., 2016). Another recent study (Shahab et al., 2017) compared, in 37 participants of traditional cigarette-only smokers, and in 72 smokers and 72 ex-smokers with long-term e-cigarette use or with use of NRT, the exposure to nicotine, tobacco-related carcinogens and toxicants. Urine and saliva samples were collected and there were no differences in salivary or urinary biomarkers of nicotine intake after controlling for confounders. The study found lower carcinogen and toxicant levels in participants who had switched completely from smoking to either exclusively e-cigarettes or NRT use. However, both of the studies, conducted by Pulvers et al. and Shahab et al., used samples too small to assess the potential association of different types of e-cigarettes, did not assess indirect exposure and were limited by the number of biomarkers available.

A large study used data from 5,105 of the U.S. adults participating in the Population Assessment of Tobacco and Health (PATH) study and compared exposure to toxicants amongst e-cigarettes users, non-smokers and smokers. This study examined urine samples for key biomarkers of exposure to harmful chemicals, tobacco-specific nitrosamines (TSNAs), metals, polycyclic aromatic hydrocarbons (PAHs), and volatile organic compounds (VOCs), and suggested possible benefits for smokers who totally switched to e-cigarettes.

Exclusive users of e-cigarettes were exposed to more toxicants than people who did not use any form of traditional cigarette, but at significantly lower levels than smokers (Goniewicz et al., 2018).

E-cigarette use and cancer risk: The cancer risk related to e-cigarette usage would be expected to be less than traditional cigarettes based on the fact that e-cigarettes include nicotine but not many of the other toxicants in traditional combusted cigarettes.

On this basis their use should result in a reduced burden of carcinogens compared with smoking (Chen et al., 2017; Stephens, 2018).

A small number of studies to date have focused on e-cigarette users and cancer. For example, in a study conducted by Franco et al. (2016), oral cells were collected by scraping the oral mucosa from a population of 65 participants from three groups: traditional cigarette smokers (n = 23); e-cigarette users (n = 22); and non-smokers or users of traditional cigarettes and e-cigarettes (n = 20).

Their findings showed that compared with non-smokers of traditional cigarettes and non-users of e-cigarettes, the mean number of micronucleated cells/1,000 cells and the measure of total micronuclei/1,000 cells was respectively 160% and 633% higher in traditional cigarette smokers and 21% and 133% higher in e-cigarette users.

This study, despite not presenting any evidence on the reliability of the micronucleus assay, nor reporting all important p-values, or several potential confounding factors (e.g. age, or age at smoke initiation), showed that the average micronuclei burden was high in e-cigarette users compared with never smokers, and was higher in traditional cigarette smokers compared with e-cigarette users and never smokers.

A further study assessing RRs compared with smoking was conducted by Manzoli

et al. (2017). They enrolled 932 participants at BL assessment with the following sample sizes at the end of the 24-month follow-up: 363 smokers of only traditional cigarettes throughout follow-up, 97 users of only e-cigarettes throughout follow-up, and 37 dual users of both traditional and e-cigarettes. This study reported the definition “any cancer” as one of the possible serious adverse events (SAEs) in participants with this distribution: 0.8% (3/363) in traditional cigarettes users, 2.1% (2/97) in e-cigarettes users and 0% (0/37) in dual users. The risk ratios calculated from these data, using traditional cigarettes as the referent category, were 2.49 (95% CI 0.42-14.72) for e-cigarettes only and 0 (95% CI not estimable) for dual use. Considering that all participants were previous traditional cigarette users, the findings did not provide any indication of elevated cancer risk from sole use of e-cigarettes. However, the study did have limitations including: the absence of consideration of traditional cigarette smoking history, a small sample size to evaluate the endpoint of cancer, and self-reported cancer data.

Studies in humans focusing on cancer and e-cigarette use are relatively few in number, and to date there are no epidemiological studies on the possible association between e-cigarette use and cancer in humans. This makes it difficult to draw definitive conclusions about any association between e-cigarette use and risk of cancer in human populations. However, a joint statement on e-cigarettes by Public Health England and other UK public health organisations (PHE, 2016) developed a shared agreement document stating that e-cigarettes are significantly less harmful than smoking. A recent study conducted by Stephens (2018) measured emissions from cigarettes and e-cigarettes, calculating lifetime cancer risk using daily consumption estimates, and calculated that e-cigarette cancer potencies were largely found to be only a small fraction of those of smoking (0.4%).

E-cigarette use, respiratory and heart conditions: A different body of research has focused on e-cigarettes’ effects on users of traditional cigarettes with or without pre-existing respiratory conditions such as COPD or asthma. These studies in humans examine the effect of switching to e-cigarettes (single or dual use), examine health effects of e-cigarettes compared with traditional cigarette usage, and overall suggest that smokers with pre-existing respiratory conditions such as asthma and COPD may experience some benefits from switching to e-cigarettes (Polosa et al., 2014 a, b, 2016 a,b; Campagna et al., 2016; Cibella et al., 2016). Our research

group in Italy has contributed to this literature on respiratory health and e-cigarettes. In a one-year RCT of healthy smokers who abstained from cigarette smoking and switched to e-cigarette use, we observed improvements in their exhaled breath measurements, including fractional nitric oxide concentration in exhaled breath (FeNO) and exhaled carbon monoxide (eCO) (Campagna et al., 2016). A 24-month prospective study (Polosa et al., 2016) demonstrated improved respiratory symptoms and lung function in 16 former smokers who switched to e-cigarettes, suggesting that e-cigarette use could potentially contribute to reversing the harm from combustible tobacco in smokers with asthma. Polosa et al. (2017), conducted a study with young-adult never-smoking, daily e-cigarette users who were followed up for at least 3½ years by our research group. No worsening in spirometric indices (i.e. lung function), no development of respiratory symptoms, no changes in markers of lung inflammation in exhaled air, and no signs of early lung damage on high resolution computed tomography (HRCT) were detected. However, a limitation of these studies is that they were conducted in a small number of smokers selected retrospectively from the same region and primarily from a single study research group, which limits generalizability of the results. Different findings come from a high-quality RCT with large sample size, where Cravo et al. (2016) reported no difference in lung function in smokers who switched to e-cigarettes. In this study smokers with respiratory conditions were excluded and two cohorts of smokers were randomised to either change to e-cigarettes with nicotine or continue smoking traditional cigarettes. The authors reported no significant positive or negative changes in pulmonary function tests after 12 weeks between the two groups (Cravo et al., 2016). Several recent studies have evaluated acute cardiovascular effects such as modifications in blood pressure (BP) levels and HR (HR) following e-cigarette use. Studies investigated modifications in BP levels after e-cigarette use (Farsalinos et al., 2014a; Szołtysek-Bołdys et al., 2014; Yan and D’Ruiz, 2015; Cooke et al., 2015; Fogt et al., 2016; Moheimani et al., 2017). These studies had some inconsistent results, with the majority finding weak positive increases or no modifications and harms using e-cigarettes. Previous studies, using first and second generation e-cigarettes, found no changes in HR following e-cigarette use (Vansickel et al., 2010; Farsalinos et al., 2014a; Szołtysek-Bołdys et al., 2014) but these were conducted with devices characterized by slight or no increase in blood nicotine levels. In one prospective study, using first and second generation e-

cigarettes and conducted by our team in Italy, systolic BP was significantly reduced at week 52 compared with BL (132.4 +/- 12.0 vs. 141.2 +/- 10.5 mmHg, $p < 0.00$) amongst participants who had reduced smoking (>50% reduction) and in those who had quit smoking with the use of e-cigarettes. These findings suggest that e-cigarette use does not elevate BP (Farsalinos et al., 2016). This study did not find any changes in BP when assessing all participants, because the vast majority initially had normal BP and no change in this parameter was expected to occur within the 12-month duration of the survey. The interest was directed towards the population with an initially high BP (high-normal or higher, as defined by the European Society of Cardiology). The reduction in BP was evident even after adjusting for confounders such as age, gender and weight gain. However, these early studies may not reflect the effects of newer devices. Some more recent research using third generation devices, which increase blood nicotine levels, has identified some increase in HR just after e-cigarette use (Cooke et al., 2015; Spindle et al., 2017; St. Helen et al., 2017). A key factor to consider when drawing any conclusions about potential health risks from e-cigarettes is the extent to which studies directly compare vaping with tobacco smoking. Those studies that have aimed to directly compare the two have fairly consistently found reduced levels of harm if participants switch completely to vaping from smoking. Looking across the body of literature, there is convincing evidence that vaping amongst ex-smokers reduces exposure to toxicants that are carcinogenic and may increase the risk of cancer. In addition, there is now good evidence that risks to both cardiovascular (Yan and D’Ruiz, 2015; D’Ruiz et al., 2017) and respiratory health (Polosa et al., 2014a,b; 2016b,c) are reduced when smokers switch from using combustible tobacco to vaping.

2.3 E-cigarette use and craving

Smokers with considerable histories of cigarette usage report using e-cigarettes to alleviate nicotine withdrawal generated by smoking cessation or to satisfy cravings for these traditional cigarettes (Etter and Bullen, 2014).

An RCT (Adriaens et al., 2014) on smoking behaviour and use e-cigarettes in 48 traditional cigarettes smokers randomised participants into two e-cigarette groups and one control group.

One of the researchers' objectives was to assess whether e-cigarettes decreased craving in the short term, and during the laboratory studies in the first two-month period of the study, researchers assessed craving and found that e-cigarettes proved to be just as effective in suppressing the craving for smoking as traditional tobacco cigarettes.

Dawkins and Corcoran (2014) enrolled 14 experienced vapers and asked them to abstain overnight from their traditional cigarettes. In the morning, they were presented with a first-generation e-cigarette with 18 mg/mL nicotine, from which they were invited to take 10 puffs. As a result, the nicotine craving and urge to smoke were significantly reduced in these participants. In a second study, Dawkins et al. (2016) presented 63 abstinent smokers who were not current e-cigarette users with either a red or a white first generation e-cigarette containing 18 mg/mL of nicotine in the form of "tobacco" flavored e-liquid after a 10-hour abstinence period. Their results suggest that the visual appearance of an e-cigarette has an effect on cigarette craving reduction. These researchers found that the more the e-cigarette resembled a traditional cigarette, the stronger the craving reduction.

Another study focused on e-cigarettes' flavour (Goldenson et al., 2016) and showed that nicotine-free and nicotine-containing e-cigarettes produced greater appeal when containing sweet flavours than when containing non-sweet flavours or no flavour.

2.4 E-cigarettes and smoking cessation

Smoking is a difficult addiction to break and many smokers persist in tobacco use for numerous years, typically cycling through multiple periods of remission and relapse (Caponnetto et al., 2013a; Caponnetto et al., 2013b). Yet, while complete cessation of any nicotine use may be the most desirable final outcome, substitution of traditional cigarettes with alternative non-combusted forms of nicotine delivery, such as e-cigarettes, is now a relatively new option available to smokers. Surveys of e-cigarette users have examined reasons for use and, overall, these suggest that users report using them to help quit smoking, to reduce cigarette consumption, to

relieve tobacco withdrawal symptoms, and to continue some of the behavioural aspects of smoking with perceived reduced risks to (Etter, 2010).

2.4.1 Early studies of e-cigarettes for smoking cessation

The first RCT examining the impact of e-cigarettes on smoking behaviour was conducted by the research team at the Centro per la Prevenzione e Cura del Tabagismo-University of Catania (CPCT), Italy, led by Professor Riccardo Polosa and including the PhD candidate. This study found that smokers not immediately willing to quit who used e-cigarettes substantially decreased daily cigarette consumption without significant side effects (Caponnetto et al., 2013c). The trial involved 300 smokers without mental health conditions recruited from advertisements in a local newspaper in Catania. This double blind RCT examined the effects of using a 7.2 mg nicotine e-cigarette, hereafter referred to as Group A; 7.2 mg for six weeks, then transition to 5.4 mg nicotine e-cigarettes, hereafter referred to as Group B; and nicotine-free e-cigarettes, hereafter referred to as Group C, on smoking reduction/cessation and adverse effects. The primary outcome of the study was >50% reduction in cigarettes/day (CPD) at the 52-week study visit from BL. The secondary outcome was sustained smoking abstinence at the 52-week study visit.

The eligibility for study inclusion was adult smokers in good health, age 18-70 yrs., using ≥ 10 factory-made CPD for at least the past five years, not attempting /wishing to quit in the next 30 days. Exclusion criteria for the study were symptomatic CVD, symptomatic respiratory disease, regular psychotropic medication use, current or past history of alcohol abuse, use of smokeless tobacco or NRT, pregnancy or breastfeeding. Participants were not encouraged or given any motivation to cease smoking. Study participants were instructed to use the product ad libitum throughout the day, not to exceed a four cartridge/day maximum as recommended by the manufacturer of the product. Participants attended follow-up visits at 2, 4, 6, 8, 10, 12, 24, and 52 weeks. At each of these visits, participant eCO levels were recorded, study diaries were given to study personnel, and unused study products were turned in. After 12 weeks, no additional cartridges were provided to the participants. However, participants were told they could continue to use the e-cigarettes. Saliva

cotinine levels were measured at six and 12 weeks in participants who reported no smoking and had an eCO \leq seven ppm.

Loss to follow-up was 35/100 (35%) in Group A, 37/100 (37%) in Group B, and 45/100 (45%) in Group C. All patients were analyzed in the group to which they were first allocated with an intention to treat philosophy. At week 52, 10/100 (10%) of those allocated to Group A, 9/100 (9%) of those allocated to Group B and 12/100 (12%) of those allocated to Group C had reduced their CPD by \geq 50%, $p = 0.24$. At week 52, 13/100 (13%) of those allocated to Group A, 9/100 (9%) of those allocated to Group B and 4/100 (4%) of those allocated to Group C had achieved smoking abstinence and had eCO concentrations of \leq seven ppm, $p = 0.24$. Self-reported adverse effects amongst the remaining 183 participants of the study at 52 weeks included: throat irritation 37/183 (20.2%), mouth irritation 34/183 (18.6), dry cough 37/183 (20.2%), headache 5/183 (2.7%), shortness of breath 15/183 (8.1%). No SAEs (that is, major depression, abnormal behaviour or any event requiring an unscheduled visit to the family practitioner or hospitalization) occurred during the study.

The second RCT examining the impact of e-cigarette use on smoking behaviour was conducted by the research team at the National Institute for Health Innovation, University of Auckland and Health New Zealand, Christchurch, led by Professor Chris Bullen (2013). This research evaluated the quitting efficacy, acceptability, and adverse effects of e-cigarettes, comparing active (16 mg nicotine) e-cigarettes with nicotine patch and placebo (0 mg nicotine) e-cigarettes. The trial was a three-arm parallel group RCT. A total of 657 smokers were randomised into one of three groups: a group who used active e-cigarettes for 12 weeks after quitting, a group using nicotine patches for 12 weeks, or a group using placebo e-cigarettes for 12 weeks. Quit rates were assessed at three and six months after the quit date. The primary outcome was the proportion of smokers who maintained sustained continuous abstinence from smoking for six months after their quit day. Secondary outcomes were: continuous abstinence at one and three months, seven-day point prevalence, proportion of participants who significantly reduced daily cigarette smoking by at least 25% in terms of numbers of CPD, and AEs.

Those eligible for study inclusion were adult smokers in good health, age ≥ 18 yrs, who had smoked at least 10 cigarettes per day for the past year and were motivated to stop smoking. Exclusion criteria for the study were: having had a heart attack, stroke or severe angina in the previous two weeks; poorly controlled asthma or other airway disease from self-report; poorly controlled diabetes mellitus; severe allergies; poorly controlled psychiatric disorders; or current drug dependence other than that involving nicotine. Pregnant and breastfeeding women were excluded.

At six months, the verified continuous abstinence was 7.3% (21 of 289) with nicotine e-cigarettes, 5.8% (17 of 295) with nicotine patches, and 4.1% (three of 73) with no-nicotine e-cigarettes. No significant difference between e-cigarette users compared with nicotine patch users was found in six-month abstinence rates (RR 1.26, 95% CI = 0.68 to 2.34).

A significantly higher proportion of e-cigarettes users, compared with nicotine patch users, achieved a 50% or more reduction in traditional cigarette use (57% vs 41%; RR 1.41, 95% CI 1.20 to 1.67). The first group reduced traditional cigarette consumption by an average of 9.7 (SE 0.4) CPD, compared with a reduction of 7.7 (SE 0.4) showed by nicotine patch users ($P = 0.002$). The authors noted no evidence of an association between AEs or SAEs and products used in their study.

There are also non-randomised studies of e-cigarettes for smoking cessation and this literature is too extensive to summarise those here.

2.4.2 Systematic reviews of e-cigarettes for smoking cessation

Following these early studies, a large number of subsequent studies have been published focusing on e-cigarettes for smoking cessation. These have been summarized and assessed in a number of systematic reviews; in fact, there are 22 systematic reviews of e-cigarettes for smoking cessation published to date.

The most robust of these is the Cochrane review of e-cigarettes for smoking cessation, first published in 2014 and subsequently updated in 2016. In this Cochrane review of the effect of e-cigarettes on smoking cessation, Hartmann-Boyce et al. (2016) identified 24 studies: two RCTs that followed participants for at

least six months (described in section 2.3.1 above) and 22 observational studies which followed participants for less than six months or did not put people into treatment groups so could not directly compare e-cigarettes with something else. The authors also identified 15 ongoing trials. The two RCTs compared e-cigarettes with and without nicotine and had a combined sample size of 662 participants (Bullen et al., 2013; Caponnetto et al., 2013c). One trial included minimal telephone support, one recruited smokers not intending to quit, and both used early e-cigarette models with low nicotine content and poor battery life. In the meta-analysis of the two trials, e-cigarettes had a higher smoking cessation rate compared with placebo e-cigarettes. Nine percent of participants using an e-cigarette containing nicotine successfully quit for at least six months compared with 4% of participants using a placebo e-cigarette (RR 2.29, 95% CI 1.05 to 4.96). Also, in this review, none of the studies found that smokers who used e-cigarettes short- to mid-term (for two years or less) had an increased health risk compared with smokers who did not use e-cigarettes.

Hartmann-Boyce et al. (2016) judged the RCTs to be at low risk of bias, though they rated the overall quality of the evidence as 'low' or 'very low', because of imprecision due to the small number of trials. According to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system used in Cochrane reviews, a 'low' grade means that further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate. A 'very low' grade means there is uncertainty about the estimate.

The WHO commissioned El Dib et al. (2017) to conduct a systematic review and meta-analysis of the effect of e-cigarettes on traditional cigarette use amongst smokers. This research compared e-cigarettes with nicotine with e-cigarettes without nicotine and two independent reviewers, who also extracted data and assessed the studies' risk of bias, independently evaluated prospective observational studies published up to December 2015. Three eligible randomised trials were considered, with 1,007 participants, but the third randomised trial was excluded because the effect of e-cigarettes versus no e-cigarettes couldn't be compared for 24 weeks; hence, a total sample of 481 participants were considered. These researchers also identified nine eligible cohort studies with 13,115

participants but concluded overall that there was still limited evidence about the effectiveness of e-cigarettes for smoking cessation.

These two systematic reviews considered a similar group of studies and arrived at similar conclusions: that the available studies are few and that additional evidence is needed to provide a definitive conclusion. However, the reviews differed slightly in their interpretation. The Hartmann-Boyce (2016) systematic review found a statistically significant effect of nicotine e-cigarettes compared with e-cigarettes without nicotine and considered this an important effect of e-cigarettes on quitting, and El Dib et al. (2017), using the same studies, were more cautious in their conclusions.

Kalkhoran and Glantz (2016) conducted a systematic review and meta-analysis and identified 38 eligible studies about the impact of e-cigarette use on smoking cessation amongst adult smokers. In this systematic review and meta-analysis, the authors included cohort studies, cross sectional studies, and randomised and non-randomised clinical trials published up to December 2015 and concluded that e-cigarettes are associated with significantly less quitting amongst smokers (Kalkhoran & Glantz, 2016).

Khoudigian et al. (2016) published a systematic review and meta-analysis of RCTs and observational studies about smoking cessation for at least 24 weeks after the start of e-cigarette adoption. These authors observed that despite their findings, which suggested that e-cigarettes with nicotine increased the proportion of smokers who quit (RR of 2.02 (95% CI = 0.97-4.21), this change was not statistically significant in their meta-analysis. Consequently, the authors concluded that several larger high-quality studies are needed to inform policy decisions.

In conclusion, the existing systematic reviews on e-cigarettes for smoking cessation have inconsistent results. However, all identify the need for further research, in particular further RCTs.

2.4.3 More recent studies of e-cigarettes for smoking cessation

Since the trials, observational studies and systematic reviews mentioned above were conducted, there have been furthermore recent studies on e-cigarettes for smoking cessation. In particular, three recent population-based, cross sectional studies have been conducted that identify promising smoking cessation rates, particularly amongst more frequent e-cigarette users (Levy et al., 2017; Zhu et al., 2017; Giovenco & Delnevo, 2018).

Firstly, Giovenco & Delnevo (2018) conducted a retrospective cohort study by including smokers and former smokers who quit in 2010 or later. Amongst these participants daily e-cigarette users and former smokers were 52%, daily e-cigarette users and never e-cigarette users were 28%, (adjusted prevalence ratio (aPR) 3.15, 95% CI = 2.66, 3.73). Compared with participants who never used e-cigarettes (aPR 0.38, 95% CI = 0.32, 0.47), those who previously used e-cigarettes but did not use them currently and those who used them on only some days were less likely to be former smokers (aPR 0.67, 95% CI = 0.61, 0.75).

In addition, Levy et al. (2017) retrospectively generated a cohort of smokers who were using traditional cigarettes one year prior to their survey. This research focused on the association between e-cigarette use and having made a quit attempt in the past year, and having been abstinent from traditional cigarettes for a minimum of 12 weeks after a quit attempt. By using multiple logistic regression analysis, their findings suggested that: quit attempt in the past year was related to previous or current e-cigarettes usage and that the probability of smoking cessation for 12 weeks or more was significantly associated with e-cigarette use.

Finally, in terms of the most recent studies, Zhu et al. (2017) examined data from the large U.S. Current Population Survey-Tobacco Use Supplement (CPS-TUS). The researchers drew on survey data from more than 160,000 respondents to generate a retrospective cohort of participants who reported having been smokers of traditional cigarettes one year prior to the survey. They examined the population-level rates of making a quit attempt in the past year and of quitting smoking. Smokers who used e-cigarettes during 2014-15 were more likely than non-users to make a quit attempt and obtain complete smoking cessation. The analysis verified that the quit rates between smokers of traditional cigarettes who used or had ever

used an e-cigarette showed a smoking cessation rate increased by 1.1 percentage points between 2010-2011 and 2014-2015. This happened in coincidence with the increase of e-cigarette use amongst smokers of traditional cigarettes. Hence, in this study e-cigarettes appear to have helped to improve smoking cessation rates.

All three of these more recent studies have significant limitations. They are observational in nature and thus cannot determine causality. In addition, there was likely to be recall bias amongst participants in relation to both the extent of e-cigarette use and quit attempts. Finally, there may be confounders not assessed in the studies, including lack of information on previous quit attempts, the type of e-cigarette used, motivation to quit and reasons for e-cigarette use, for example.

In a very recent fourth study, e-cigarettes usage was almost twice as effective as NRT to help smokers of traditional cigarettes quit smoking (Hajek et al., 2019). This multicentre randomised trial of e-cigarettes versus NRT involved 886 adults attending smoking cessation services in England. The smokers were randomised with 447 individuals assigned to a NRT group and 439 assigned to an e-cigarette group. Both groups received one-on-one behavioural counselling each week for four weeks and were biochemically tested at the end of the year to assure they had stopped smoking. Smokers in the e-cigarette group were given a starter pack, a 30 mL bottle of tobacco flavoured e-liquid with a nicotine concentration of 18 mg per mL, and instructions on how to use the device. Participants were encouraged to use different flavoured e-liquids with different concentrations of nicotine. Participants in the NRT group were offered a several products including patches, gum, lozenges, nasal or mouth sprays, inhalers, mouth strips, or microtabs and they were encouraged to choose a combination of products.

The primary outcome was sustained smoking abstinence for one year, which was biochemically validated during the final visit of the trial. Secondary outcomes included participant-reported treatment usage and respiratory symptoms. The researchers observed a one-year abstinence rate of 18.0% in the e-cigarette group compared with 9.9% in the NRT group. This study found that 80% of participants in the e-cigarette group were more likely to continue using their product at one year compared with 9.0% in the NRT group. This study had several strong points, including long-term outcomes with a large sample size, a real life setting,

researchers who let participants choose their e-liquid and their NRT, biochemical verification of smoking cessation outcomes, and rigorous data analysis but it's uncertain if the results would generalize to other populations of smokers. It is also not possible to affirm that these discoveries would apply to other e-cigarette devices, or away from the setting of a controlled study and lacking behavioural counselling.

2.5 E-cigarettes for smoking cessation in people with schizophrenia spectrum disorders

While the number of studies examining e-cigarettes for smoking cessation in the general population is now fairly substantial, despite mixed conclusions, there are far fewer studies relevant to this topic that have been conducted with priority groups for smoking cessation. This includes people with schizophrenia spectrum disorders: the population that is the focus of this thesis. This section reviews the existing published literature on this topic, firstly outlining findings of studies that have examined e-cigarettes as an intervention for smoking cessation in this group, and secondly outlining the prevalence and attitudes of people with schizophrenia spectrum disorder regarding e-cigarettes.

2.5.1 Interventional studies

When initial work on this PhD thesis began, there was almost no available literature on e-cigarettes for smoking cessation for smokers with schizophrenia. The exception was a small uncontrolled study conducted at CPCT, where the PhD candidate is based. This was the first study in the world to investigate the efficacy of e-cigarettes for smoking cessation/reduction in people with schizophrenia.

In this early study, 14 smokers with schizophrenia spectrum disorders not motivated to quit smoking were recruited. Fourteen smokers were provided with an electronic cigarette kit and enough cartridges to last up to 12 weeks. They were advised to use the product ad libitum throughout the day, not to exceed a four cartridge/day maximum as recommended by the manufacturer of the product, a first generation "Categoria" e-cigarette, (Arbi Group Srl, Milano, Italy) loaded with 7.4 mg nicotine cartridges called "Original" cartridges. Participants were followed-up for one year. At each visit, participant eCO levels were recorded, study diaries were given to study personnel and unused study products were turned in. Overall, this study found that

at the 52-week visit, 50% of smokers with schizophrenia who were provided with e-cigarettes for 12 weeks had reduced their smoking by 50%, and a further 14% had quit smoking completely with no increases in psychiatric symptoms (Caponnetto et al., 2013d). These preliminary findings are noteworthy because none of the participants initially sought treatment for smoking. However, the study had a significant number of limitations, including the absence of a control group and a very small sample size.

Subsequently, Pratt et al. (2016) enrolled 21 outpatients with serious mental illness (schizophrenia, schizoaffective disorder, or bipolar disorder) who smoked at least 10 CPD, had a history of failed treatment-facilitated quit attempts, and were not involved in smoking cessation treatment. Participants were given second generation e-cigarettes (N-Joy brand) based on each participant's level of use of traditional cigarettes and directions on how to use them, and were evaluated weekly for one month. Authors declared that each e-cigarette cartridge was approximately equivalent to two packs of traditional cigarettes but they didn't mention the nicotine strength of the cartridges used in the study. Nineteen participants completed the study visit (10 with schizophrenia spectrum disorders, nine with bipolar disorder). The study found a significant smoking reduction with a mean self-reported decline in use of traditional cigarette from 192 to 67 cigarettes/week confirmed by CO reduction from 27 ppm to 15 ppm. There were some AEs reported: 58% of participants experienced mild and transitory side effects, including cough, dry/sore throat, nausea and dizziness. The study also examined participant's perceptions. In answer to open-ended questions, these smokers perceived e-cigarettes as enjoyable and satisfying, and they were willing to buy e-cigarettes; they also perceived e-cigarettes as healthier, useful to help them feel more accepted by non-smokers, and useful to avoid the unpleasant odor of burned cigarettes. In their conclusions Pratt et al. suggested that people with serious mental illness may find e-cigarettes an appealing alternative to traditional cigarettes but recommended that further RCTs with longstanding mental health conditions were needed.

In a more recent study, Hickling et al. (2018) conducted a 24-week pilot study to investigate the efficacy of a six-week free first-generation e-cigarette treatment to reduce traditional cigarette consumption in 50 smokers with severe mental illness

not motivated to quit, including 42 (84%) participants with schizophrenia spectrum disorders. These smokers were offered free NJOY disposable e-cigarettes with 4.5% nicotine and were encouraged to replace traditional cigarettes with e-cigarettes as much as possible. A final follow-up visit for assessment was scheduled at week 24. At the end of the six-week free e-cigarette phase, 37% of participants had reduced their tobacco consumption and 7% had stopped smoking. Four weeks post this phase 26% of participants had reduced their tobacco consumption and 5% had quit to smoke traditional cigarettes. At final follow up (24 weeks), 25% of participants had reduced their tobacco consumption and 2% had quit to smoke traditional cigarettes. This study found good product acceptability and no negative impact on participants' mental health or significant AEs. However, the study had limitations, including that 16% of participants with bipolar disorder had their psychopathological changes assessed by the PANSS scale, which is designed to assess schizophrenia spectrum disorder symptoms and not bipolar disorder symptoms. In addition, as the authors acknowledged, the study was also limited by the fact that it involved the use of a first-generation e-cigarette, considered less effective in terms of blood nicotine delivery, and the use of a self-report method for various measures.

2.5.2 Prevalence and attitudes towards e-cigarettes in people with schizophrenia spectrum disorders

In addition to a small number of intervention studies, there are also some data available on the extent to which schizophrenic smokers use e-cigarettes and their attitudes towards these products. For example, Miller et al. (2017) investigated the prevalence and attitudes of e-cigarette use in the USA amongst 60 inpatients and outpatients with schizophrenia or schizoaffective disorder diagnosis.

Participants completed an anonymous, 10-minute, pencil-and-paper survey to evaluate the prevalence of and attitudes toward e-cigarette use, and use of e-cigarettes to help or hinder their psychopathology. The majority (70%) of participants were current smokers, of whom 83% smoked a mean of 15 CPD; 90% percent of participants were aware of e-cigarettes, 37% had used them, 7% were current users and 24% of never-users were considering using e-cigarette in the future. Thirty four percent of surveyed smokers believed that the health effects of e-cigarettes were less harmful than traditional cigarettes.

Cost was the most frequently mentioned potential disadvantage of e-cigarettes (33%) and health improvements (39%), smoking reduction (37%), and quitting (37%) were the most commonly mentioned potential benefits.

Smokers who were ever-users stated that traditional cigarettes were significantly more useful in reducing paranoia, anxiety, depression, and reduced concentration, than e-cigarettes.

The authors suggested that e-cigarettes have modest significance to smoking cessation in smokers with schizophrenia spectrum disorders and concluded that their preliminary findings should be investigated in larger samples.

Chen et al. (2016) conducted a survey of smoking cessation treatment with 231 smokers with serious mental illness (33% with schizophrenia/schizoaffective disorders, 63% with mood disorders, 11% with post-traumatic stress disorder and eight percent with borderline personality disorder), 45 psychiatrists and 97 case workers in four community mental health centers in the USA.

Fifty percent of smokers showed an interest in using e-cigarettes to quit smoking and 22% reported current e-cigarette use. There were differences between patient and provider perspectives: despite 82% of patients reporting wanting to quit or reduce traditional cigarette smoking, 91% of psychiatrists and 84% of case workers stated that their patients were not interested in quitting; hence, psychiatric treatment providers perceive their patients to have no motivation to quit smoking.

In contrast, their patients reported motivation to use and active use of e-cigarettes to quit smoking.

Sharma et al. (2017a) conducted a qualitative study to analyze Reddit online lay discussions and assess motivations and limitations associated with e-cigarette use amongst people with self-reported mental illness, including nine smokers with schizophrenia. Their thematic analysis included 3,263 comments from 133 discussion threads.

Motivations to use e-cigarettes amongst people with mental illness included self-medication, quitting smoking, freedom and control, as a hobby, for social connectedness and in response to caregivers and online communities. Some limitations of e-cigarettes use included that they were perceived to be an

unsatisfactory substitute for traditional cigarettes and psychiatric medicines, drug interactions, nicotine addiction, risks of e-liquid, practical difficulties and cost.

2.6 Summary and conclusion

Following on from the introductory chapter, this second chapter has reviewed further relevant literature to provide context for the thesis. It began by describing the concept of THR and then discussed the development of e-cigarettes and their characteristics. The chapter also summarised and critically reviewed studies on the RRs of e-cigarette use compared with smoking as well as available literature on vaping as a smoking cessation strategy in the general population and then for smokers with schizophrenia spectrum disorders.

Although e-cigarettes have not been proven to be totally safe, evidence reviewed in this chapter suggests that they may be less harmful alternatives to combustible cigarette smoking. Consequently, e-cigarettes could be considered as an applicable instrument for THR. This chapter also outlined the history, evolution and marketing of e-cigarettes and existing evidence on e-cigarette harms and benefits. While tests of e-cigarette constituents, in vitro toxicological tests, and short-term research in humans suggest that e-cigarettes are likely to be less harmful than traditional cigarettes, due to absence of long-term epidemiological research and large clinical trials, the consequences for long-term effects on health and death are not yet clear. As a result, the safety of e-cigarette use cannot be definitely assessed at this time.

A further directly relevant theme for this thesis, however, is whether the existing literature suggests that e-cigarettes can help smokers to quit. Systematic reviews of e-cigarettes for smoking cessation in the general population suggest mixed results, but the best quality review (Cochrane) and one other show promising findings. These need to be confirmed in future trials. Smokers with schizophrenia spectrum disorders and new routes to smoking cessation are the main focus of this thesis. Overall, there are very few studies of e-cigarettes for smoking cessation in patients with schizophrenia and these studies are very small. They have promising results, but more research is needed. The findings from these studies, conducted with first generation and second-generation e-cigarettes, suggests that the provision of e-cigarettes can significantly reduce traditional cigarette consumption and CO expired

breath without significant variations of psychopathological signs and symptoms and without showing significant and serious AEs. There is little research about the views and perceptions of this group of people regarding e-cigarettes as an acceptable aid to quitting or reducing smoking. The next chapter describes a qualitative study of people with schizophrenia spectrum disorders who smoke and their views about traditional cigarettes compared with e-cigarettes and the appeal of licensed cessation aids compared with e-cigarettes for smoking cessation or smoking reduction.

CHAPTER 3: QUALITATIVE STUDY

3.1 Study title: A qualitative study of the views about smoking, licensed cessation aids and e-cigarettes in people with schizophrenia spectrum disorders

3.2 Chapter overview

This chapter presents a qualitative study which explored the perspectives of 30 participants with schizophrenia spectrum disorders about traditional cigarettes compared with e-cigarettes, and licensed cessation aids and e-cigarettes for smoking cessation or smoking reduction. Half of the participants were motivated to quit and half unmotivated to quit. This chapter includes a description of the purpose of the study, research questions, methods, findings and interpretation. I have used the principles of the Standards for Reporting Qualitative Research (SRQR) guidelines to structure this chapter.

3.3 Purpose of the study

This is the first qualitative study to explore the perspectives about traditional cigarettes compared with e-cigarettes and the views about licenced cessation aids and e-cigarettes for smoking cessation or smoking reduction in an exclusive sample of participants with a DSM-V diagnosis of schizophrenia spectrum disorders. It is also the first to explore the similarities and differences amongst this group according to their motivation to quit. Views about smoking cessation treatments may be different according to motivation. It is arguably important to understand this through a comparative combined analysis between motivated and not motivated smokers in order to improve and tailor interventions and inform the protocol for a future RCT (Chapter 5). There are several qualitative studies about the experience of smoking, smoking cessation or reduction and smoking cessation aids in people with schizophrenia spectrum disorders (Knowles et al., 2016; Rae et al., 2015; Esterberg & Compton, 2005), all discussed in Chapter 1. When my PhD studies began, there were no published qualitative studies of adult smokers with schizophrenia spectrum disorders regarding e-cigarettes for smoking cessation or smoking reduction. Since then, Sharma et al. (2017a) has conducted a thematic analysis about the motivation to use e-cigarettes and their limitations using postings made by 1,681 people with

mental illnesses on the Redditt website. These authors analysed 3,263 comments from 133 discussion threads, of which 2.1% (n = 9) were made by people who self-reported they had schizophrenia.

3.4 Research questions

Research questions included the following:

- How do people with schizophrenia spectrum disorders perceive traditional cigarettes compared with e-cigarettes?
- How appealing are licenced cessation aids for smoking cessation or reduction?
- How appealing are e-cigarettes for smoking cessation or reduction?

3.5 Methodology

A qualitative approach was used for this study allowing for the exploration of the meaning of smoking, licenced medications and e-cigarettes for smoking cessation and reduction, through personal description of experiences and perspectives (Flick, 2006).

Qualitative research is a method of enquiry, based on the report of events gained through observation or interaction with participants, to gain an in-depth understanding of human behaviour. It draws from the situation in which events occur and attempts to “describe occurrences, as a means of determining the process in which events are embedded and the perspectives of those participating in the events, using induction to derive possible explanations based on observed phenomena” (Gorman, 2005, p.3).

Qualitative information is collected by audio recording, video recording, and transcribed texts from interviews with single participants or focus groups. Induction, the method of understanding and interpreting information, and the presentation of participants’ viewpoints are created after data and evidence have been collected (Braun, 2006).

There are various methodological approaches for conducting qualitative research, depending on the purpose of the study and the research questions. A

phenomenological approach served as a guiding methodology in the development of this study, having considered other common methodologies, described in Table 1. A phenomenological approach seeks to discover how individuals construct meaning of the human experience (Moerer-Urdahl & Creswell, 2004) and represents the lived experiences of those being interviewed. Discovering the essence of the respondents' perspective improves accuracy in representing the phenomenon (Moustakas, 1994). During the process of qualitative research, the researcher is obliged to develop a broad foundation of relative knowledge in order to examine adequately the developing themes (Strauss & Corbin, 1998).

Table 1: Examples of qualitative methodologies

| Methodology | Brief description |
|--------------------|--|
| Phenomenology | Describes the "lived experience" of a phenomenon and the meaning, structure and essence of the lived experience. The researcher tries to gain access to an individual's world, i.e., their world of experiences, which is where consciousness exists (Moerer-Urdahl & Creswell, 2004). |
| Grounded Theory | The development of inductive "bottom-up" theory that is grounded directly in the empirical data. Each new individual observation is compared with existing data to identify similarities and differences (Charmaz, 2006). |
| Ethnography | Ethnography is the study of behaviours, social connections, and perceptions that naturally occur within groups or communities. The principal aim is to provide in-depth insights into people's views and actions by collecting detailed observations and interviews (Hammersley & Atkinson, 2007). |

This qualitative study is based on an interpretive paradigm, which advocates from a theoretical perspective the study of research participants' experiences, which are taken at face value. Behaviours that stem from experiences help describe reality. Interpretation can be achieved by exploration of recordings or quotations through the formulation of categories against which a text is analysed (Gorman, 2005). The interpretive paradigm sees each experience and situation as unique with its

meaning being an outcome of the circumstances as well as the individuals involved (Moustakas, 1994). Moustakas (1994) identified seven common qualities of an interpretive paradigm. These are:

1. Focusing on the wholeness of an experience instead of its parts.
2. Formulating questions and problems that reflect the interest, involvement, and interpersonal and personal commitments of the researcher.
3. Obtaining first person accounts of experiences through (in)formal discussions and interviews.
4. Putting value on qualitative designs and methodologies as approaches to human experiences.
5. The day-to-day experience is imperative to understanding human behaviour and can be used as evidence for scientific research.
6. Searching for underlying meanings of experiences rather than simple measurements or explanations.
7. Experience is integrated into an inseparable relationship between subjects and objects either in part or whole.

3.6 Methods

The following sections provide an account of the eligibility criteria, and methods for recruiting participants and collecting data. Thematic analysis was used to analyse, synthesise and interpret the data.

3.6.1 Eligibility criteria

Participants were eligible for the study if they

1. Had a diagnosis of schizophrenia spectrum disorder according to DSM-V criteria, with first or multiple episodes. A homogenous diagnostic sample (i.e. only people with schizophrenia) was preferred to a heterogenous one (e.g. people with bipolar disorder, depression and anxiety) because people with schizophrenia have similar patterns of thinking, emotion and behaviour compared with people with other mental disorders. People with schizophrenia also have a higher co-morbidity between smoking and schizophrenia compared to other mental disorders (de Leon and Diaz, 2005).

2. Were outpatients who were in the stable phase of illness (no relapse or hospitalization in the previous three months and/or need to change psychopharmacological treatment in the previous month (Mendrek et al.2012)), to ensure a state of absence of psychopathological exacerbation in line with studies conducted in people with schizophrenia (Potvin et al., 2013; Bourque et al., 2013).
3. Were current smokers of ≥ 10 CPD for at least the past five years. My research group in Catania has used this criterion in previous studies with e-cigarettes (Caponnetto et al., 2013c, Russo et al., 2016). Our rationale for this criterion in these two Italian studies was influenced by our intention to provide help for the 'average Italian smoker' and provide a potentially effective intervention generalizable to all smokers. We therefore used the data from the Statistical Observatory on Smoking in Italy; the average daily number of cigarettes per Italian smokers was 13, with higher prevalence from 25 to 65 years and an average age at initiation of 18 (OSSFAD, 2012).
4. Were aged 18 to 65 years.
5. Had not used licenced smoking cessation aids or e-cigarettes as part of an intention to modify their daily cigarette consumption (to a quit or reduce) in the previous 12 months. The rationale for this eligibility criterion is based on the evidence that recent use of cessation aids could in some way significantly change their appeal and perception (Perez Mata et al., 2017). Product usage may influence attachment to the product and its associated appeal and perception (Klein & Baker, 2004; Ball & Tasaki, 1992). Product attachment has been defined as "the emotional bond a consumer experiences with a product" (Schifferstein & Zwartkruis-Pelgrim, 2008). Norman (2004) holds that the attachment between the user and product is formed by product appearance and aesthetic appeal, behavioural-product in use, effectiveness and pleasure of use and personal satisfaction of using it. A study showed that recently acquired and used products (under one year) have a high level of attachment for users (Schifferstein & Zwartkruis-Pelgrim, 2008). Use and frequency of e-cigarettes was assessed following recommendations by Pearson et al. (2017).

Motivation to quit was assessed by two answers of the Motivation to Stop Scale (MTSS) (Kotz et al., 2013). The MTSS consisted of one item and participants were asked "Which of the following describes you?"

The seven answers of the MTSS offer a dimensional vision of the motivation to quit smoking, from 1=lowest to 7=highest level of motivation to stop (1. "I don't want to stop smoking"; 2. "I think I should stop smoking but don't really want to"; 3. "I want to stop smoking but haven't thought about when"; 4. "I really want to stop smoking but I don't know when I will"; 5. "I want to stop smoking and hope to soon"; 6. "I really want to stop smoking and intend to in the next three months"; 7. "I really want to stop smoking and intend to in the next month"), but not a categorical one and do not allow a precise demarcation or cut-off between those who are motivated and those who are not motivated to quit. Hence, I identified participants clearly not motivated to quit to be people who answered "*I don't want to stop smoking*". I considered participants clearly motivated to quit as people who answered "*I really want to stop smoking and intend to in the next month*". The first answer correlates with the absence of any belief or desire to quit, the second answer correlates with a strong desire and short-term intention to quit (Kotz et al., 2013). I explored the perception of motivated participants and unmotivated participants to understand the commonalities and differences between the two groups and the possible implication for smoking cessation and/or THR.

3.6.2 Setting

All interviews were conducted at Catania Schizophrenia Center, Department of Mental Health. The Department of Mental Health is part of the Italian National Health System (SSN) and is responsible for prevention, psychiatric diagnosis, care and rehabilitation and for the organisation of interventions aimed at safeguarding the mental health of the local population. The Department of Mental Health aims to eliminate any form of discrimination, stigma and exclusion directed at persons with a mental disorder or condition, and actively promotes the full and complete rights of citizenship of such persons. The Department of Mental Health guarantees that the mental health services and structures operating within the SSN constitute a single and unified organisational structure. Further, the Catania Schizophrenia Centre

ensures the close coordination between its services and other SSN districts. This Centre cares for people who are outpatients. I carried out the qualitative study between October 2016 and January 2017 prior to the single arm pilot study (Chapter 4).

3.6.3 Sampling and recruitment strategy

In this study, I used two non-probability sampling techniques, namely purposive sampling and quota sampling, which complemented each other.

Purposeful sampling is widely used in qualitative research (Patton, 2002). In this type of sampling, participants are selected or sought after according to pre-selected criteria based on the research question (i.e. the eligibility criteria). Quota sampling is a sampling technique whereby a participant quota is pre-set prior to sampling (an equal number of motivated and unmotivated participants). The sample size was predetermined: 30 smokers with schizophrenia were recruited according to their motivation to quit smoking. According to Creswell (1998) five to 25 participants are required for qualitative phenomenological studies; as I had two subgroups, I chose to recruit 15 participants for each group. I also aimed to capture both breadth and depth of understanding from men and women. Fifty-five people were referred for assessment for inclusion in the study, 10 were excluded because they did not meet the eligibility criteria (smoked fewer than 10 CPD), and 15 were excluded because they scored in the middle range of MTSS. It was easier and quicker to recruit clearly unmotivated than clearly motivated participants and as such, these participants were enrolled first in the study.

3.6.4 Ethical issues

The qualitative study was approved by the University of Stirling ethics committee on 24 October 2016 (Appendix 1). Participants gave written informed consent prior to participation in the study. The recruitment and informed consent process was consistent with that for clinical research (Appendix 2, Appendix 3). Clinicians (psychiatrists, clinical psychologists, nurses, and clinical social workers) from the Schizophrenia Center informed current patients about the study and if agreeable arranged a suitable time for interview with the researcher. I enrolled them into the study if they met the eligibility criteria and informed consent was then taken by the

researcher before the interview began. This means that the referring clinician had no knowledge of whether the person he or she nominated participated or not.

Participant data were stored securely on a University password protected computer. Interview recordings were transcribed verbatim and anonymised, with participants identified by a unique identification number. Audio recordings will be retained for at least three years after the completion of the research (and stored in a locked filing cabinet). Only anonymous versions of transcripts were shared with the PhD supervisors, to help guide plans for the analysis. This qualitative study considered the dimensions of non-biological risk (e.g., psychosocial, anxiety-related, confidentiality, disclosure, stigmatization, and legal issues) that are associated with taking part in this research. It was important that study participants with schizophrenia (who were all volunteers) had an intellectual understanding of the overall goals of the research. I also considered the phenomenon of “respondent burden” (e.g. time, energy, and emotional expenditure of participants). The recruitment and informed consent process presented in the next section describes how I considered ethical issues and the strategy to mitigate any risks. With any interview there is a small risk that the participant may disclose information that causes the researcher concern for the participant’s safety or that of someone else. It was not anticipated that interviews would precipitate potentially sensitive content; however, it was made clear when obtaining informed consent that participants could refuse to answer any questions they wished and could terminate the interview at any time (with no reason necessary). If during the interview the participant became distressed, he or she was offered a break, offered to terminate the interview or steered to discuss another topic. It was made clear that everything he or she said was confidential unless he or she disclosed to the researcher something that caused concern for his or her own safety or others’ safety. I used a structured topic guide and took care to direct the conversation back to this if the participant discussed something that was not relevant or particularly sensitive.

3.6.5 Data collection and processing

Individual structured interviews were used to collect data, conducted by two trained clinical psychologists at a Schizophrenia Center. This included me (the PhD student) and another colleague (Dr Marilena Maglia), who interviewed some female patients

who were more comfortable with a female interviewer. Neither of us had any previous knowledge or clinical relationship with any of the participants. I chose to use a structured interview to facilitate data collection. People with schizophrenia spectrum disorders may be suspicious, have difficulty with attention and concentration, or have poverty of thought or in some cases logorrhoea; a structured approach provides more focus for both interviewer and interviewee compared with an unstructured or semi-structured approach. The interviews followed a structured topic guide developed by me with input from my supervisors (Appendix 4) and covered the following aspects: smoking history; mental health experience; views about the taste, satisfaction and cost of traditional cigarettes and e-cigarettes; the perceived impact of both on their health; their knowledge and experience of NRT, varenicline and bupropion; and the appeal of e-cigarettes and licenced cessation aids for smoking cessation or reduction.

A topic guide is a structured series of topics which reflect the objectives of the interview. During the creation of this topic guide, I kept in mind the specific research questions and I followed guidelines by Ulin et al. (2004) for constructing a topic guide. As suggested by King and Horrocks (2010), in constructing this topic guide I used my own personal experience in the research area and consulted the research literature on the subject. Hence, as the first step I identified topics and subtopics. The key topics were extracted from the original research questions and these were broken down into subtopics. As a second step, I chose the sequence of the topics and subtopics to direct the natural flow of the conversation. As the final step, I prepared opening and closing statements.

Interviews took place during working hours at the Schizophrenia Center in a private room where no one else was present; all interviews were recorded. The duration of the interviews ranged from 10 minutes to one hour and the average length of interviews was approximately 15 minutes (some participants became distressed or were easily fatigued, which influenced the length of the interview). I transcribed all interviews verbatim within one week of each interview. It took an average of two to four hours to transcribe each interview script. Transcription can be problematic because, depending on the length of the interview, nuance can be lost via the omission of non-verbal cues such as pauses, laughter, anger and pitch which can

be important aspects of the analysis (Cohen et al., 2011). The use of a tape recorder was very helpful in this regard as it gave me the opportunity to consider these para-verbal cues more fully when transcribing. I initially transcribed the interviews in Italian and then translated the transcripts into English. Several of the participants had opted to use Sicilian or both Italian and Sicilian language during the interviews, which made the transcription and translation complex at times, especially as I had to ensure that I did not distort any of the information presented by the participants.

3.6.6 Analysis

I approached this study using thematic analysis, which involved multiple angles and iterations of studying the participants' views. Braun & Clarke (2006) describe thematic analysis as "a method for identifying, analyzing and reporting patterns (themes) within data" (Braun and Clarke, 2006, p. 6). They also describe it as a flexible and useful research tool that provides a rich and detailed, yet complex, account of the data (Braun & Clarke, 2006). Thematic analysis involves the search for and identification of common threads that extend across an entire interview or set of interviews (DeSantis & Noel Ugarriza, 2000) in which a 'theme' is the main product of data analysis (Green et al., 2007).

Thematic analysis is different from other qualitative methods of analysis in that "thematic analysis is not wedded to any pre-existing theoretical framework and therefore it can be used within different theoretical frameworks" (Braun & Clarke, 2006 p. 9). Following the six-phased guide suggested by Braun & Clarke (2006) (Figure 3), the first step in thematic analysis involves becoming closely familiar with the data by reading and re-reading the interview transcripts. This included my translation of the transcriptions from Italian into English, validating the transcriptions through reading a translated transcript and listening to its corresponding audio recording. The English transcriptions were sent to my second supervisor (Dr Deborah Robson) for independent reading. I then studied the transcripts one at a time (Appendix 5), actively engaging the text through highlighting and memoing different sections, and then generating one- to two-page summaries on each smoker.

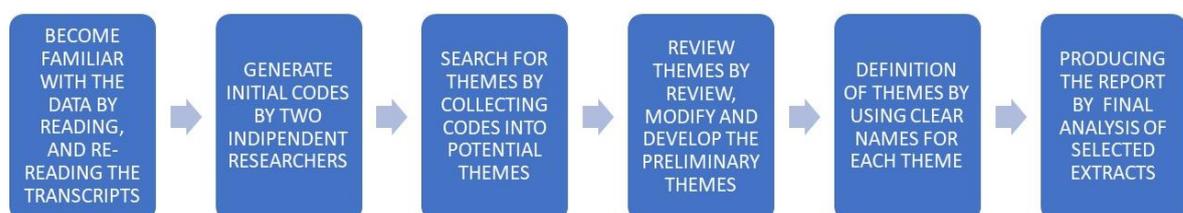
Following the close reading phase, my second supervisor and I independently made notes and developed a coding system that comprised deductive codes derived from

the topic guide (e.g. financial cost of smoking) and inductive codes that emerged from the interview data (e.g. the experience of time). This involved examining the data while keeping the research question at the forefront of my mind, noting down additional material that might not be directly related to the question but that provided a context to understanding the participant's experiences. Using NVivo software, we coded sections of text in the transcript that aligned with the descriptions of the code as well as the surrounding context. In this process, we regarded our codes as filters for the large amounts of textual data in that they organized sections of text around a common description. Once the codes were applied to all of the transcripts, we re-organized the codes into themes.

In thematic analysis a theme is defined as “a pattern found in the information that at a minimum describes and organises the possible observations and at a maximum interprets aspects of the phenomenon” (Boyatzis, 1998, p. 4). Four broad themes were identified and related to the original research question: 1) reasons for starting to smoke; 2) perceptions of traditional cigarettes compared with e-cigarettes; 3) perceptions and appeal of licensed medications for smoking cessation or reduction; and 4) the appeal of e-cigarettes for smoking cessation or reduction.

While all transcript data are required in order to arrive at the themes, it is not necessary to use all the data to illustrate the theme. The quotations used need to capture discrete aspects of the themes. The presentation of each theme requires a process of writing and re-writing. The final phase can be described as the process of synthesis (Braun and Clarke, 2006). Once each theme was clearly defined and described, I illustrated the theme with reference to the transcripts using extracts of verbatim quotations and photographs of study participants in order to capture the essence of the theme.

Figure 3. Six-phased guide suggested by Braun & Clarke



3.6.7 Data Management

I began arranging data in a systematic manner whilst still conducting field work. I typed my field notes every day, transcribed the interviews, downloaded photographs from my camera and attached memos accordingly. I used NVivo 11, a Computer Aided Qualitative Data Analysis Software (CAQDAS) programme, to manage the data. The use of the NVivo software facilitated the process of organising, re-arranging and managing the considerable amount of data. The interview transcripts were formatted in Microsoft Word to facilitate importing the transcripts into NVivo. Importing transcripts into NVivo, resulted in the questions being displayed in the content panel in the NVivo explorer. Hence, when selecting a question, it was possible to jump to this section in the interview transcript. After coding the interviews in NVivo, all passages assigned to a specific code were viewed on screen and printed. I also had access to each participant's biographical data and these were kept under a node classification file. An advantageous feature of NVivo is that the software keeps a log of all data that were entered, which means that all codes and memos were automatically assigned a date and time stamp. This feature helped to trace the development of codes. I took photographs (with the participants' consent) with the intention of using them to enrich the illustration of potential themes. These were stored in a password protected external file.

3.7 Findings

This section begins with a description of the participants' characteristics, then gives a tabulated overview of the themes followed by a more detailed synthesis.

3.7.1 Participant characteristics Thirty interviews were conducted with 20 male and 10 female participants; their characteristics are presented in Table 2. Fifteen participants were not motivated to quit smoking and 15 participants were motivated to quit smoking.

Table 2: Characteristics of participants

| | Total (n=30) | Not motivated to quit (n=15) | Motivated to quit (n=15) |
|--|-------------------------|---|---|
| Gender male: n (%) | 20 (67%) | 10 (67%) | 10 (67%) |
| Gender female: n (%) | 10 (33%) | 5 (33%) | 5 (33%) |
| Age: mean years (SD) | 46.4 (12.2) | 49.3 (10.5) | 43.4 (13.2) |
| Age of onset of schizophrenia spectrum disorders: mean years (SD) | 19.2 (1.8) | 19.5 (1.7) | 18.9 (1.9) |
| CPD: mean (SD) | 25.1 (11.1) | 23.8 (12.4) | 26.3 (10.4) |
| Age of onset of smoking: mean years (SD) | 17.1 (5.2) | 17.5 (4.4) | 16.6 (5.9) |
| Length of time smoking: mean years (SD) | 30.3 (13.4) | 33.7 (12.8) | 26.3 (13.7) |
| Packs/year: mean (SD) | 37.8 (22.9) | 39.5 (25.1) | 36.1 (25.2) |
| Participants who have previously tried to quit: n (%) | 9 (30%) | 1 (6.7%) | 8 (54.4%) |
| Ever e-cigarette users: n (%) | 15(50%) | 6 (40%) | 9(60%) |
| Former daily e-cigarette users: n (%) | 10 (33.3%) | 4 (27.2%) | 6 (40%) |
| Previously ever used a licenced cessation aid: n (%) | 1 (3.3%) | 0 | 1 (6.6%) |
| NRT | 1 (3.3%) | 0 | 1 (6.6%) |
| Varenicline | 0 | 0 | 0 |
| Bupropion | 0 | 0 | 0 |

Participants who were not motivated to quit had similar smoking and clinical characteristics for gender and age of smoking initiation, were slightly older and had smoked for longer compared with those who were motivated to quit. People who were motivated to quit smoked more CPD and had previously tried to quit more times than those who were not motivated to quit smoking. Half of the total sample had a history of ever e-cigarette use (according to the definition by Pearson et al., 2017), with slightly more participants from the motivated group having ever used them. A third of the total sample were classified as former daily e-cigarette users (according to Pearson et al., 2018), again slightly more in the motivated group. Only one participant (from the motivated group) had ever previously used NRT as a

licensed cessation aid. No one had previous experience of using varenicline or bupropion for cessation.

3.7.2 Themes

Participants' views were synthesised into four themes and related codes (Table 3).

Table 3: Themes and codes

| Theme | Codes |
|--|--|
| Reasons for starting to smoke | <ul style="list-style-type: none"> • Age initiation • Social context • Why start smoking? |
| Perceptions of traditional cigarettes compared with e-cigarettes | <ul style="list-style-type: none"> • Taste • Satisfaction • Enjoyment • Financial cost • The experience of time • Perceived impact of traditional and e-cigarettes on health |
| Perceptions and appeal of licensed medication for smoking cessation or reduction | <ul style="list-style-type: none"> • Experiences of NRT for quitting or reduction • Experiences of Varenicline for quitting or reduction • Experiences of Bupropion for quitting or reduction • Intention for future use |
| The appeal of e-cigarettes for smoking cessation or reduction | <ul style="list-style-type: none"> • Experience of e-cigarette use for quitting • Experience of e-cigarette use for reduction • Perceptions of harm Intentions for future use |

3.7.2.1 Theme 1: Reasons for starting to smoke

Participants in both groups started to smoke when they were teenagers and before their diagnoses of schizophrenia spectrum disorders. When asked to recall their reasons for smoking initiation, only two participants could not remember why they started. Many participants said they started smoking with friends (n = 11) whilst still

at school or with family members (n = 4). They started smoking to rebel, feel like an adult, be cool, or be attractive, or during a period of sadness.

| REASONS FOR STARTING TO SMOKE | |
|--|---|
| Not motivated to quit smoking | Motivated to quit smoking |
| <i>"I started smoking because everyone smoked, my mother too."</i> (Cetty, female, aged 58) | <i>"I started to smoke during a sad period"</i> (Mela, female, aged 55). |
| <i>"I started smoking to be cool"</i> (Sharon 60, female, aged 39) | <i>"I started smoking because i felt bad, i felt sad. I wanted to be a rebell"</i> (Gino, male, aged 29) |

3.7.2.2 Theme 2: Perceptions of traditional cigarettes compared with e-cigarettes

Participants were asked about their views about traditional cigarettes and e-cigarettes in relation to the taste, satisfaction, enjoyment, cost, experience of time, and impact on their health and wellbeing.

Taste, satisfaction and enjoyment

The two groups held mixed opinions about the taste and satisfaction of traditional cigarettes. Compared with the motivated participants, participants who were not motivated to quit considered the taste of traditional cigarettes as an important part of their smoking experience and they preferred particular brands over others. The majority (n = 13) of the unmotivated participants enjoyed the taste of traditional cigarettes and found them satisfying compared with a minority of the motivated group (n = 4). Most participants in the motivated group no longer experienced satisfaction from smoking; they reported they smoked because they were addicted to tobacco and found it too difficult to quit.

| TASTE, SATISFACTION AND ENJOYMENT OF TRADITIONAL CIGARETTES | |
|---|---------------------------|
| Not motivated to quit smoking | Motivated to quit smoking |

| | |
|--|--|
| <i>"ohh....It's a big part of my life....if It wasn't for the cigarettes, I could not do anything in the day"</i> (Glenda, female, aged 55) | <i>"Smoking is an addiction, not a satisfaction"</i> (Bruno, male, aged 57) |
| <i>"I don't like the taste of the cigarette filter, I take out the filter to feel the taste of cigarettes"</i> (Julietta, female, aged 25) | <i>"Though it's a bad habit, smoking is nice"</i> (Tony, male, aged 37) |

Participants had a range of experiences with regards to e-cigarette use. Half the total sample had never used an e-cigarette and therefore were not asked about the experience of taste and satisfaction. The 15 participants who had ever used an e-cigarette (six from the unmotivated group and nine from the motivated group) expressed different opinions about e-cigarettes. Very few participants in both groups who had previous experience of having tried an e-cigarette liked the sweet taste of some products, though one person preferred tobacco flavor. The majority across both groups said either they did not like the taste of e-cigarettes or preferred the taste of traditional cigarettes. A minority across both groups were satisfied by their previous e-cigarette use. Another aspect they emphasized was the complexity of using an e-cigarette compared with a traditional cigarette and the effort required.

| TASTE, SATISFACTION AND ENJOYMENT OF E-CIGARETTES | |
|--|--|
| Not motivated to quit smoking | Motivated to quit smoking |
| <i>"I only smoked the e-cigarettes for two days, it's ok, you can choose from different flavors such as vanilla, cinnamon, and it smells good.... but it doesn't give you the same satisfaction as normal cigarettes"</i> (Glenda, female, aged 55) | <i>"I've tried an e-cigarette for a while but I sometimes broke the atomizer...e-cigarettes take long time to charge and only five minutes to smoke so I had a complicated relationship with them."</i> (Giorgia, female, aged 44). |
| <i>"It's less powerful than my cigarettes"</i> (Ugo, male, aged 55) | <i>I used them in the past and it was satisfying"</i> (Natale, male, aged 28) |

Financial cost

The majority of participants in the motivated-to-quit group reported that they thought traditional cigarettes were too expensive, whereas only half of the unmotivated group believed they were expensive and the other half were not worried about the cost. Some participants bought hand rolled tobacco as a way to save money. The 30 participants spent approximately €216 (SD 91.6) per month on traditional cigarettes. In Italy people with schizophrenia receive approximately €250 per month from the National Institute of Health (SSI). Therefore, smokers with schizophrenia spend the majority of the money they receive from the SSI to buy cigarettes.

| COST OF TRADITIONAL CIGARETTES | |
|--|---|
| Not motivated to quit smoking | Motivated to quit smoking |
| <p><i>“Yes, they are expensive, I spend €300 a month”</i> (Enrico, male, aged 43)</p> | <p><i>“I think they are too expensive, they cost €20 euro...one packet of 20 cigarettes, you can't buy anything else”</i> (Carla, male, aged 58)</p> |
| <p><i>“The costs are not a problem, but now they are increasing”</i> (Julietta, female, aged 25)</p> | <p><i>“Now cigarettes are more expensive than before..... the cost is increased. I started smoking hand rolled tobacco, that is more cheap than traditional cigarettes”</i> (Gino, male, aged 29)</p> |

All participants were asked their opinion about the cost of e-cigarettes and their views varied. Eleven participants (five from the unmotivated group and six from the motivated group) considered e-cigarettes to be less expensive than traditional cigarettes. Nine participants (five from the unmotivated group and four from the motivated group) did not know how much e-cigarettes cost and the remainder thought they were more expensive (one from the unmotivated group and four from the motivated group) or a similar cost. The majority of those who had no previous experience of e-cigarette use were unaware of the costs.

| COST OF E-CIGARETTES | |
|--|--|
| Not motivated to quit smoking | Motivated to quit smoking |
| <i>“E-cigarettes are more expensive...they are waste of money” (Ugo, male, aged 55)</i> | <i>“I know that the price is around 50-60 euros” (Rosa, female, aged 39)</i> |
| <i>“Considering the battery cost, considering the e-liquid cost, the overall costs are the same more or less, with little differences (Enrico, male aged 43)</i> | <i>“They are a waste of money and time” (Giorgia, female, aged 44)</i> |

The experience of time

Smoking traditional cigarettes was seen as a way to structure time and occupy the day. Participants reported that other people were less likely to interrupt you whilst you were smoking and respected their personal time compared with time spent vaping; they suggested that other people were more likely to interrupt you or ask you to do something while vaping and assume that you could re-start vaping any time.

| TRADITIONAL AND E-CIGARETTES AND THE EXPERIENCE OF TIME | |
|--|---|
| Not motivated to quit smoking | Motivated to quit smoking |
| <i>“With a cigarette there is a beginning and an end.... you must finish a cigarette. The e-cigarette finishes when I finish the liquid... and at the end with a normal cigarette I can understand where my time goes...and this doesn't happen using an electronic cigarette” (Juliette, female, aged 25)</i> | <i>“A positive thing about (traditional) cigarettes is that it punctuates the times of my days....With the cigarettes you have 5 minutes to yourself and no one disturbs you, you have a break from the rest of the world, others only disturb you if there is an important situation.....when you are using the e-cigarette other people disturb you for minor things, this does not happen when you smoke cigarette” (Pippo, male, aged 27)</i> |

Perceived impact of traditional and e-cigarettes on health

Participants in both groups were aware that smoking traditional cigarettes causes several diseases. The group who were not motivated to quit perceived traditional cigarettes as damaging to their physical health but did not express concern; instead they described smoking as helpful, calming and as a way to cope with negative emotions. This is in contrast to the group who were motivated to quit, who were

concerned that smoking might damage their physical health, for example by causing respiratory problems such as cough, sore throat, catarrh and bronchitis or cancers.

The majority of participants from the unmotivated group (n = 9) were not aware of the impact of vaping on health. Three participants considered e-cigarettes safer than traditional cigarettes and three participants considered them dangerous for their health. In the group who were motivated to quit, many (n = 8) considered e-cigarettes safer than traditional cigarettes for their health and the remainder either believed e-cigarettes were dangerous or not useful to improve their health or were unaware. Participants reported that smoking traditional cigarettes had a positive effect on their mental health, helping them feel less anxious and depressed and relieving stress. None of the participants from either group mentioned a similar effect from an e-cigarette.

I interviewed exclusively smokers of traditional cigarettes. On the other hand, if I had interviewed a group of daily vapers, they may have said that e-cigarettes had a positive effect on their mental health.

| PERCEIVED IMPACT OF TRADITIONAL AND E-CIGARETTES ON HEALTH | |
|---|---|
| Not motivated to quit smoking | Motivated to quit smoking |
| <p><i>“Smoking is dangerous, we all know this, but I have a personal trick, I don’t breathe in the smoke, I just taste the tobacco...If you breathe in the smoke it will go into your lungs and be dangerous for you”</i> (Sara, female, aged 58)</p> | <p><i>“Normal cigarettes give you a lot of body illness for example cancer, but with the help of the modern science you can get rid of this.... but it would be better to not smoke at all”</i> (Natale, male, aged 28)</p> |
| <p><i>“I smoked four packs a day in the past then I felt sick and I had a cardiac arrest.... I started to smoke again but not as much as before”,</i> (Sharon female, aged 60)</p> | <p><i>“A few months ago, I suffered with bronchitis and stopped for three weeks, but I started again”</i> (Grace, female, aged 65)</p> |
| <p><i>“Smoking helps me with my depression, (traditional) cigarettes make me feel better”</i> (Sara, female, aged 58)</p> | <p><i>“I obviously think it’s is a bad thing, it’s supposed to help your stress, but actually it ends up making stress worse, it’s very bad for you”</i> (Pippo, male, aged 27)</p> |

3.7.2.3 Theme 3: Perceptions and appeal of licensed medication for smoking cessation or reduction

Participants were asked to describe their perceptions of NRT, varenicline and bupropion. Ten motivated-to-quit participants compared with nine non-motivated participants had heard of NRT patches and gum but all participants in both groups were not aware of varenicline and bupropion. Three participants from the motivated group had heard about some other approaches to help smokers quit other than pharmacotherapies. One participant had heard about psychotherapy, another suggested acupuncture and a third participant was aware of liquorice sticks (an alternative therapy).

Nicotine replacement therapy

The majority (n = 19) were aware of NRT but only one participant had ever tried it in the past. A similar number of participants in both groups were aware of NRT (10 in the motivated group and nine in the unmotivated group); however, most participants in both groups believed NRT was ineffective for helping smokers quit smoking or reduce cigarette consumption. Participants in the motivated group had a variety of views; one participant reported that when using NRT previously that participant had experienced nausea, gastritis and headaches. Other participants believed that NRT was only helpful for occasional smokers and not regular smokers, was too expensive and only benefitted pharmaceutical companies. Participants in the unmotivated group suggested that NRT was only effective for a brief period of time and others thought it increased the amount one smoked.

One participant in the motivated group expressed an interest in using NRT in the future to help quit and two to help reduce their cigarette consumption. Most were interested in using a nicotine patch, gum or mouth spray and their choice was influenced by either the cost of the product or what they had seen on TV. One participant in the unmotivated group expressed curiosity about the possible effects of the mouth spray.

| PERCEPTION AND APPEAL OF NRT | |
|--|--|
| Not motivated to quit smoking | Motivated to quit smoking |
| <i>“NRT helps you to quit for a very brief period of time, for example for an hour”</i> (Glenda, female, aged 55) | <i>“I’ve never used a nicotine patch because I was worried about the cost”</i> (Giorgia, female, aged 44) |
| <i>“Many smokers who use the patch smoked even more. I have never tried them”</i> (Enrico, male, aged 43) | <i>“The patches satisfy half of your nicotine needs and are good for occasional smokers and not for regular smokers, because it cannot satisfy their nicotine needs”</i> (Nino, male, aged 38) |

Bupropion

None of the participants had heard of bupropion. After I gave them brief information about it as a licensed smoking cessation aid, no participants in the unmotivated group wanted to use it to quit or reduce smoking. The information below was provided according to principles of the “Standard Treatment Programme: A guide to behavioural support for smoking cessation” (McEwen, 2014).

“Bupropion was the first non-nicotine medication available to smokers and research shows that, like NRT, it doubles your chances of successfully stopping. Bupropion is an antidepressant tablet that works by reducing urges to smoke and other withdrawal symptoms once you have stopped smoking. It does have some common minor side effects that include headache, difficulty sleeping and dry mouth; and some more serious side effects”.

Four participants in the motivated group expressed an interest in bupropion as a smoking cessation tool because they believed bupropion’s antidepressant effects might help them with their mood problems; however, they were also slightly concerned about the possible adverse effects. An additional participant in the motivated group expressed an interest in using bupropion to reduce cigarette consumption.

| PERCEPTION AND APPEAL OF BUPROPION | |
|--|--|
| Not motivated to quit smoking | Motivated to quit smoking |
| <i>“No, I don’t want to spend more money and I don’t want to quit”</i> (Julietta, female, aged 25) | <i>“Yes, I would use it to quit tobacco smoking because it is an antidepressant too”</i> (Mela, female, aged 55) |
| <i>“I only want to smoke my cigarettes, I don’t want to smoke bupropion”</i> (Marco, male, aged 50) | <i>“If it doesn’t give me physical problems, I would use it”</i> (Rosa, female, aged 39) |

Varenicline

None of the participants had heard of varenicline. After I gave them brief information about it as a licensed smoking cessation aid, no participants in the unmotivated group wanted to use it to quit or reduce smoking. The information below was provided according to principles of the “Standard Treatment Programme: A guide to behavioural support for smoking cessation” (McEwen, 2014).

“Varenicline has been specifically designed to help smokers to stop smoking and initial evidence suggests that it might be the most effective of the three medications. Champix is a tablet that works by reducing urges to smoke and other withdrawal symptoms once you have stopped smoking. It also blocks the ability of nicotine to stimulate the brain which is why many smokers using varenicline do not feel ‘satisfied’ should they have a cigarette. Varenicline has some common minor side effects that include nausea, headache, difficulty sleeping and abnormal dreams”.

Only one participant from the motivated group considered it might be helpful in the future for quitting and another participant for future use for smoking reduction. One participant from the unmotivated group did not want to spend money to quit smoking; others were concerned about the effect of varenicline on their health or did not want to take additional medication on top of their psychiatric medication.

| PERCEPTION AND APPEAL OF VARENICLINE | |
|--|---|
| Not motivated to quit smoking | Motivated to quit smoking |
| <i>"No I' never heard about them"</i> (Salvo, male, aged 50) | <i>"I don't think drugs will help, I already take a lot of drugs daily I would not take more in order to quit smoking"</i> (Natale, male, aged 28) |
| <i>"They are not effective to help you to quit"</i> (Angelo, male, aged 30) | <i>"If it's safe I will use it"</i> (Mela, female, aged 55) |

3.7.2.4 Theme 4: The appeal of e-cigarettes for smoking cessation or reduction

As discussed above, only half the participants had ever used an e-cigarette previously, six in the group who were not motivated and nine in those motivated to quit (and not in the past 12 months). The total sample was ambivalent about the potential appeal of e-cigarettes as a smoking cessation or reduction tool. In the group not motivated to quit smoking, one participant believed that e-cigarettes were potentially useful for quitting and three for reduction. The general view of the remaining 11 participants in this group was that they are not an effective solution for changing their own or others' smoking behaviour. One reason given for their appeal was to save money, and another to "detox the body from nicotine".

Twelve participants from the motivated group believed that e-cigarettes were potentially useful for quitting or reducing smoking (nine for quitting, three for reducing). The remaining three participants did not find e-cigarettes (or a licensed product) appealing for either cessation or reduction.

In participants who were former daily e-cigarette users (n = 10), e-cigarettes were appealing to nine participants, six in the motivated and three in the unmotivated group. Participants who reported that they might be appealing for cessation or reduction believed they were less risky for one's health and they enabled switching from a "bad habit" to a "good habit." They reported that the physical and behavioural experience of vaping was similar to smoking in terms of the hand to mouth action and were cheaper. Participants who did not consider e-cigarette use appealing had been influenced by their physician or from negative experiences of others or what they had learned from the TV and media.

| THE APPEAL OF E-CIGARETTES FOR SMOKING CESSATION | |
|---|--|
| Not motivated to quit smoking | Motivated to quit smoking |
| <i>“They can help people that smoke a few cigarettes, not people like me that smoke a lot of cigarettes per day“</i> (Ugo, male, aged 55) | <i>“In my opinion it is not good, they are worse than normal cigarettes, my doctor told me”</i> (Davide, male, aged 25) |
| <i>“The pharmacist told me if I smoke a cigarette and an e-cigarette together, I could go into a coma because e-cigarettes are a harmful drug”</i> (Angelo, male, aged 30) | <i>“I need the same gesture to satisfy me.....you have many options but my favorite is the sweet taste”</i> (Natale, male, aged 28) |

| THE APPEAL OF E-CIGARETTES FOR SMOKING REDUCTION | |
|--|--|
| Not motivated to quit smoking | Motivated to quit smoking |
| <i>“Because with the cigarette you can smoke easily, instead with the electronic ones you have to always suck harder....the e-cigarettes are not strong enough”</i> (Pietro, male, aged 57) | <i>“They will help to save money and I will do less damage to myself”</i> (Sara, female, aged 58) |
| <i>“They both are both addictive but e-cigarettes are more addictive”</i> (Angelo, male, aged 30) | <i>“Of course, I would you use one if it’s a cure”</i> (Mela, female, aged 55) |

3.8 Discussion

This is the first qualitative study of an exclusive group of people with schizophrenia spectrum disorders and an exploration of their views about smoking and licenced smoking cessation aids compared with e-cigarettes. Structured interviews were conducted with 30 people with schizophrenia spectrum disorders who were current smokers, half of whom were motivated and the other half not motivated to quit. A thematic analysis was conducted from responses to questions about the reasons for starting smoking and experience of traditional cigarettes compared with e-cigarettes, in addition to the appeal of licenced cessation aids or e-cigarettes for smoking cessation or smoking reduction.

Reasons for starting to smoke

The majority of participants started to smoke for similar reasons as people without a mental health condition report. Adolescents’ perceptions about smoking by peers and role models play a fundamental role in smoking initiation and positive associations to smoking, including the perception of smoking of role models (e.g.

adults and friends) and social acceptability, has been suggested as predictors for adolescents' reasons to start to smoke (Wiiium et al., 2006). The same reasons were reported in a recent Italian study (Backhaus et al., 2017). Following the social cognitive theory, adolescents shape their behaviour based on people whom they consider worthy (Bandura, 1963), and adolescents who observe role models smoking have a higher probability of smoking initiation (Poulsen et al., 2002).

A study conducted by Gonzales et al. (2008), showed that people usually smoke to decrease their stress, keep calm, feel comfortable in social situations, sustain concentration, and balance their mood. In another study conducted by Barr et al. (2008b), patients with schizophrenia believed the stimulant properties of cigarettes were very important, suggesting they associate smoking with relief from negative symptoms of schizophrenia or, more likely, from medication side effects.

Their average age of onset was approximately the same age as the general population in Italy (18.1 years) (OSSFAD, 2016). However, some international studies show most smokers with schizophrenia report they begin smoking slightly later than healthy controls. De Leon et al. (2002) compared 66 patients with schizophrenia and 51 patients with a mood disorder with 404 control subjects from a community sample. Before the age of 20, the three populations appeared to have had a similar risk of smoking initiation. However, after the age of 20, the initiation rate of daily smoking for patients with schizophrenia was higher than in patients with a mood disorder or controls.

Perceptions of traditional cigarettes compared with e-cigarettes

Sensory characteristics of smoking such as the sense of smoke in the throat, the taste and smell, and the physical acts that are integral to smoking, such as unwrapping, sharing or handling cigarettes, are important determinants of the maintenance of smoking and therefore reinforcement and dependence (Carpenter et al., 2007; Rees et al., 2012). Participants across the two groups showed different opinions about the taste and satisfaction from smoking cigarettes; participants in the group not motivated to quit considered the taste of tobacco smoke fundamental for their smoking behaviour, whereas a minority of participants who were motivated to quit enjoyed the taste. Studies conducted with healthy smokers showed that

sensorial and motor stimuli as well as flavour cues and the visual appearance of an e-cigarette may contribute to the effectiveness of e-cigarettes for craving reduction (Dawkins et al., 2016; Goldenson et al., 2016). E-cigarettes retain several important features of smoking (other than the delivery of nicotine), including similar hand-to-mouth action, behavioural rituals, and an inhaled sensory stimulus. These characteristics may make e-cigarettes potentially attractive to smokers with schizophrenia (RCP, 2016).

The costs of traditional cigarettes are relatively similar to each other (e.g. a packet of 20 cigarettes in Italy ranges between €5 and €5.50). The cost of e-cigarettes devices and e-liquid bottles/cartridges varies between manufacturers and products (e.g. in Italy costs of e-cigarette devices range from €15 for a “cigalike” model, to €50 for a personal vaporizer model, to €150 for a third generation model; whereas a 10 ml bottle of e-liquid costs approximately €4 to €6 on the basis of brand used). A third of the study sample were unaware of how much e-cigarettes cost, with the other two thirds relatively equally split as to whether they thought they were more or less expensive. It is important to understand if smokers know the average cost of e-cigarettes and how they perceive the cost; if smokers believe they are too expensive this may be barrier to future use or of attractiveness/appeal. In a recent study conducted in USA by Miller et al. (2017), sixty inpatients and outpatients aged 18 to 70 with schizophrenia completed a brief survey on e-cigarette use and reported that e-cigarette cost was the most commonly endorsed potential disadvantage associated with e-cigarettes use.

Health risk perceptions of cigarette smoking is associated with motivation to quit and cessation in non-mentally ill and mentally ill smokers (White et al., 2014; Williams et al., 2011; Filia et al., 2014). However, despite acknowledging that smoking is dangerous for their health many were not motivated to quit for health reasons. A US study assembled cohorts of 174,277 individuals with ICD-9 (ICD, Ninth Revision) diagnoses of schizophrenia spectrum disorders, provided mortality estimates for conditions causally related to tobacco use in California from 1990 to 2005, and showed that smoking-related conditions may be responsible for 50% of the deaths in smokers with schizophrenia spectrum disorders (Callaghan et al., 2014).

An alternative perspective has been demonstrated in a recent study conducted by Kowalczyk et al. (2017), where a health risk subscale from the Smoking Consequences Questionnaire was used to measure health risk perception in 67 smokers with schizophrenia and 100 smokers without schizophrenia. This study reported that smokers with schizophrenia were less likely to completely recognize the health risks of smoking than smokers without schizophrenia, despite having higher average daily cigarette use and significantly higher rates of existing pulmonary disease.

Our participants reported that smoking cigarettes had a positive effect on their mental health status (e.g. helping them feel less anxious/depressed, relieving stress) and this is in line with the study conducted by Miller et al. (2017) where 60 inpatients and outpatients with schizophrenia or schizoaffective disorder who were current or former users of e-cigarettes were recruited to complete an anonymous, 10-minute, pencil-and-paper survey to examine their prevalence of and attitudes toward e-cigarette use, and reported that their experience with tobacco cigarettes were significantly more helpful with reducing depression/anxiety, impaired concentration, and paranoia than e-cigarettes.

Our participants reported that smoking traditional cigarettes helped to structure time and occupy the day and that e-cigarettes were unable to replicate this function. Previous studies including individuals with severe and persistent mental illnesses have also found that traditional cigarettes were used to structure time and formed the core of one's daily routine (York, 1997).

The National Centre for Smoking Cessation and Training (NCSCT) briefing on e-cigarettes was created to help stop smoking services support smokers who want to use e-cigarettes for quitting and included the following anecdotal quotes as examples of differences in the experience of time when using traditional cigarettes smoking compared with vaping (McEwan & McRobbie, 2016).

"It's not like a cigarette, which you would smoke from start to finish, with an e-cigarette you can sip on it once or twice, and then put it away".

“Using an e-cigarette is different to smoking a cigarette. This usually involves taking slower and longer puffs over a longer period of time..... You may feel the need to take a few puffs on an e-cigarette at times when you would not have smoked; this is nothing to worry about and your pattern of e-cigarette use will develop over time”

“Smokers binge on nicotine, vapers graze”

Perceptions and appeal of licensed medication for smoking cessation or reduction

In healthy population smokers, licensed pharmacological treatments for smoking cessation, varenicline, bupropion and NRT, are associated with increased cessation rates compared with placebo (Cahil et al., 2014). The EAGLES study showed for the first time that the efficacy of these medications in terms of ORs was similar for smokers with or without psychiatric disorders (Anthenelli et al., 2016) and in the same study varenicline appears to be the most effective pharmacological aid for smoking cessation in smokers with schizophrenia spectrum disorders. Despite these evidence-based findings, all participants in this qualitative study had never heard of varenicline and bupropion, though many participants (n = 19) were aware of NRT patches and gum. The qualitative results indicate the need for interventions to improve awareness of licensed aids (particularly varenicline and bupropion) in this group of smokers.

The appeal of e-cigarettes for smoking cessation or reduction

A recent intervention study on the appeal of e-cigarettes in smokers with serious mental illnesses conducted by Pratt et al. (2016), provides evidence that e-cigarettes may be appealing for smokers with schizophrenia spectrum disorders. A recent patient survey conducted by Chen et al. (2016) showed that half of smokers with mental illnesses reported interest in using e-cigarettes to quit smoking. This finding is similar to our results, in which about half of participants in whole sample (16 of 30) reported interest in using e-cigarettes to quit or reduce smoking. Of these 16 participants, 12 were from the motivated group and four were from the not motivated group.

Some participants who reported that e-cigarettes may be appealing for cessation or reduction perceived e-cigarettes to be less risky for their health compared with traditional cigarettes. Research about perceptions and reasons for e-cigarette use in healthy smokers has previously demonstrated that users believe e-cigarettes are less harmful than traditional cigarettes (Tan et al., 2014; Rass et al., 2015; Pepper et al., 2015) but in other studies, conducted with smokers and non-smokers, participants considered e-cigarettes just as harmful as traditional cigarettes (Majeed et al., 2017; Timothy et al., 2017; Brose et al., 2015).

In the study conducted by Miller et al. (2017), 34% (n=18) of surveyed patients with schizophrenia believed that e-cigarettes were less harmful than traditional cigarettes. In a recent study by Spears et al. (2018), conducted with 550 adult current e-cigarette users, associations between self-reported mental health illnesses and motives for e-cigarette use and risk perceptions were explored and stratified according to smoking status. Current smokers with a self-reported mental health condition indicated thinking more about how e-cigarettes might improve their health, whereas former smokers indicated thinking less about how e-cigarettes might harm their health and rated several reasons for e-cigarettes use (e.g. less harmful than traditional cigarettes and useful to quit smoking).

Several participants in the current study reported that physicians and pharmacists had told them that e-cigarettes were dangerous or just as harmful as traditional cigarettes. Harm perceptions of health professionals may influence the health behaviours of patients (Pawlikowska et al., 2012; Osuna et al., 2018), and in my opinion all health professionals should be informed about and trained in e-cigarette use in order to avoid giving misleading information to their patients.

Motivation to quit or reduce smoking in smokers with schizophrenia spectrum disorders

This is the first qualitative study to compare perceptions about traditional cigarettes and e-cigarettes in smokers with schizophrenia spectrum disorders motivated and not motivated to quit. In this research, participants in both groups showed similar reasons for starting to smoke traditional cigarettes. The majority of participants in both groups said they either did not like the taste of e-cigarettes or preferred the

taste of traditional cigarettes. More smokers who were not motivated considered the taste of traditional cigarettes to be an important part of their smoking dependence and enjoyed the taste of traditional cigarettes compared with the motivated group. Hence, for an e-cigarette to be appealing to smokers, it should be at least as tasty as traditional cigarettes, and this should apply especially to unmotivated smokers.

Both groups, motivated and not motivated, reported that using an e-cigarette was much more complicated than using traditional cigarettes. Hence, for smokers with schizophrenia spectrum disorders, motivated and not motivated to quit, an e-cigarette that is simple and easy to use might be more acceptable.

Differences between both groups were observed about traditional cigarette costs. More participants in the motivated to quit group considered traditional cigarettes to be too expensive, compared with the unmotivated group. The group not motivated to quit, in contrast with the motivated group, reported absence of concern about smoking traditional cigarettes and described smoking traditional cigarettes as helpful, calming and a way to cope with negative emotions. For this reason, a high-performing e-cigarette might be as close to the smoking experience as possible and be particularly useful for smokers who are unmotivated to quit. Many participants of the unmotivated group considered e-cigarettes to be safer than traditional cigarettes for their health.

On the other hand, motivated-to-quit participants were concerned that smoking traditional cigarettes might damage their physical health and the majority reported that they didn't know about the possible impact of e-cigarettes on their health.

There is not a definitive consensus on whether smokers with schizophrenia spectrum disorders are less likely than those without schizophrenia spectrum disorders to want to quit smoking traditional cigarettes. One perspective is that these smokers belong to a category of so-called 'hardcore' smokers, defined as daily, long-term traditional cigarette smokers who, despite extensive knowledge of the health risks of smoking, are not motivated to quit (Warner & Burns, 2003).

An alternative perspective suggests that there is some evidence that smokers with schizophrenia spectrum disorders are as motivated to quit as the general population

(Lawn et al., 2002). However, these smokers have in the past been less likely to receive smoking cessation interventions (Siru et al., 2009). Ideally, we should include motivated and not motivated smokers in future quantitative studies but current ethics arrangements in Italy make this difficult because e-cigarettes are not licensed for smoking cessation. If a person is motivated to quit smoking, in Italy it is ethically correct to suggest licensed smoking cessation aids, and so we would not easily be able to get ethical approval for a new study using e-cigarettes.

Limitations

The findings of this qualitative study are limited for a number of reasons. The sample was relatively small and comprised smokers with schizophrenia spectrum disorders motivated and not motivated to quit (total = 30 participants) drawn from the Catania Schizophrenia Center, Department of Mental Health. Furthermore, interviews were limited in length because most participants showed signs of distress, irritability and fatigue after approximately 15 minutes of interview, and this in turn limited the depth of the data. All participants were currently receiving mental health treatment and were in a stable clinical condition at the time of interview.

Overall, the sample characteristics suggest that the views elicited in the interviews may not be representative of the broader population of smokers with schizophrenia spectrum disorders, which therefore limits the generalizability of findings derived here. The findings of this study are applicable to smokers with schizophrenia who are in a stable phase of their illness. As different settings and different psychopathological conditions may have different effects on individuals, the findings from this study should not be generalized to participants in other settings and with other stable psychopathological conditions. Findings were founded on respondents' subjective perceptions of the topic and on the researcher's subjective interpretation of these perceptions.

Thematic analysis as a method is not free from criticism: some of the literature posits that this type of analysis lacks a theoretical base when compared with other strategies (Cohen et al., 2011; Brayman, 2012).

The absence of substantial literature on thematic analysis compared with grounded theory, ethnography, and phenomenology, for example, may concern novice

researchers about how to conduct a rigorous thematic analysis (Novelli et al., 2017). Thematic analysis is disadvantaged when compared with other methods, as it does not allow the researcher to make claims about language use (Braun & Clarke, 2006). While thematic analysis is flexible, this flexibility can lead to inconsistency and a lack of coherence when developing themes derived from the research data (Holloway & Todres, 2003).

In spite of these limitations, the information provided by the current research could provide a useful starting point for further research into this neglected area of tobacco control by developing smoking cessation studies and interventions tailored to these populations' needs.

3.9 Reflexivity

My personal influence on interpreting and constructing themes should be also considered. In qualitative studies such as this, the interviewer and participant can co-generate a dataset through the process of interviewing. The next paragraph explains how my past knowledge and experience may have influenced the content of my interview questions and interpretation of findings.

Regarding my past knowledge, I obtained my second degree in Clinical and Community Psychology in 2001 at the University of Rome "La Sapienza", with a dissertation thesis on schizophrenia spectrum disorders, and started my study and clinical practice in this field a month later, when I was a clinical psychologist in a small hospital dedicated to research and treatment of schizophrenia spectrum disorders. At that time, I also started my work as a researcher and psychologist at a smoking cessation clinic of the University of Catania directed by Prof Riccardo Polosa. So, for more than 15 years my research and clinical work has been dedicated to tobacco addiction, smoking cessation and schizophrenic spectrum disorders and my curiosity to do this research stems from the desire to be able to help these people to reduce the risks associated with smoking.

During the interviews, I attempted to recognize my own biases by using reflective thinking and by writing down my impressions of each single interview instantly following that interview. I always introduced myself as a PhD student and licensed

clinical psychologist, although I was conscious of the fact that such an introduction might create an association with my role of a professional healthcare worker that could potentially influence participant responses.

Regarding my past work experience, in 15 years I've seen many people die or get sick due to their smoking behaviour. Many patients died not because of schizophrenia but because of smoking and this made me feel always very helpless. My existing expertise in these two fields (tobacco addiction and schizophrenia) helped me in recruiting participants in terms of knowing where I could best recruit eligible participants. Despite this, it took longer than expected to recruit patients because many people with schizophrenia tend to avoid interpersonal contact and meeting new people. In addition, the paranoid delusions experienced by some patients with schizophrenia made it difficult to complete the audio recording and to develop a deep rapport with the interviewer. Asociality and alogia, with reduction in speech, meant that the qualitative interviews were much briefer than would be the case in interviews with adults without schizophrenia. Interviewees also had disorganized speech (formal thought disorder) with incoherence and inability to organize ideas, loose associations (derailment) and rambling. They had difficulty sticking to one topic and it was occasionally challenging to follow their trains of thought. All these signs and symptoms are the essence of schizophrenia disease.

My experience in this area helped me to establish a therapeutic alliance with interviewees and I was able to minimize any distress, which enabled participants to share with me their experiences, and they were sufficiently cooperative. They often left sentences unfinished, acting under the assumption that 'you know how ...' (e.g. how schizophrenia spectrum disorders are treated at both inpatient and outpatient levels). Because of my position, I had to be constantly alert and rigorously reflect on how my presence shaped the conversation as well as explain to interviewees that while I may have helped several smokers with and without schizophrenia spectrum disorders and several people with or without smoking addiction, during the interviews it was different for each, and I wanted to learn from their unique experience.

Finally, my experience equipped me with insights and the ability to understand implied content, and I was sensitized to certain dimensions of the data. I was familiar with the “typical” language of people with schizophrenia spectrum disorders and aware of potential sensitivities; thus, I knew what to ask and how to ask it as well as understanding the responses in a nuanced and multileveled way. I was able to hear the unsaid, probe more efficiently, and understand hints that others might miss. While listening to their stories and later analysing them, in my mind I thought about how much I wanted to help them quit or reduce smoking and protect them from the harmful effects of smoking and how I felt may influence the delivery, analysis and interpretation of my further quantitative studies.

In relation to my experience within this qualitative study, it was imperative for me to allow interviewees to tell their stories rather than ‘push’ them in certain directions, to hear what was said rather than ignore potentially painful content, and to check how I filtered what I heard through the lens of my experience and refrain from insinuation (Padgett, 2008). However, reflecting on this study has revealed other questions. For example, my hesitation to ask intimate and deep questions became clear in the reflective process. In order to respect the time and needs of the participants, I avoided very intimate and profound questions and respected their need for silence and their strange and bizarre language and behaviour including their desire to end the interview as soon as possible.

During the interviews, thanks to this qualitative research I was able to know new aspects of both the methodology of research and the experience of the patients interviewed. I last undertook qualitative research when I was at the University of Rome, about teenagers falling in love. Since then I have only conducted quantitative research and have published about 70 scientific “quantitative” articles. The first thing I noticed is that qualitative research takes a long time and it is time with a human dimension, of a man or woman and of his/her dignity and personal quality. Compared with the initial interview scheme, which assumed about an hour per interview, the actual answers were frequently very, very short; however, I thought that the strength of qualitative research was precisely this, to get out of my schemas derived from years in quantitative research and to welcome the interviewees in their

natural quality, without imposing presetting grids, so as to uncover patients' real needs, demands and expectations.

Another feature that concerned me, but I think it is in total harmony with the pathology from which the respondents suffer, was the extreme inconsistency in some answers where an interviewee often said everything and the opposite of everything on the same subject. This incoherence at times made it difficult to understand and interpret what really mattered to the patient. During the interviews it was important to respect the psychic balance of the patient: I had to be able to obtain information without stressing the patient with excessive intrusiveness that would cause them agitation or disturbed thoughts. Another thing that struck me is that patients often did not want to talk or tended to give short and stereotypical answers because they said they were in a hurry to go to smoke. It became important to be extremely delicate with these patients to avoid being intrusive and to respect them in their unrest, in their dependence, in their equilibrium when entering their world. I was also very concerned about the non-compliance of the smoking rules by the participants, who tended to smoke even in closed places, and the extreme tolerance of the carers of these patients in allowing them to smoke, but I thought this was extremely unfair and discriminatory towards these patients because they removed the possibility of avoiding smoking-related diseases. So, it's very important to improve smoking cessation interventions for this vulnerable population. I was very concerned, perceiving that many were poor and despite this they spent all the state aid in buying cigarettes, just as I was very concerned to see their fingers and lips burned by cigarettes, their teeth stained by smoke and some clothing that carried the typical signs of cigarette burning. With permission from the subjects, I took some photos to further illustrate my findings.

Smoker's Fingers



Smoker's Clothing



Even the environments, such fundamental elements of our well-being, appeared dirty and contaminated by cigarettes. The outside garden was full of cigarette butts and some patients picked them up from the ground to smoke them. Also, the lounge of the waiting room and the tent had unmistakable signs of cigarette burning and this made me think about how many risks of fires are generated by cigarettes.

Garden at the Schizophrenia Center



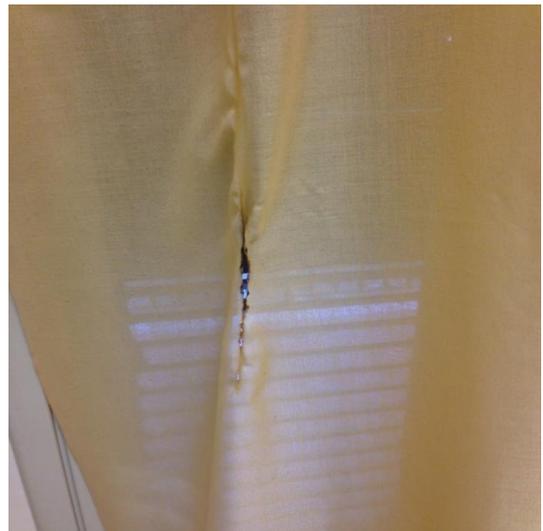
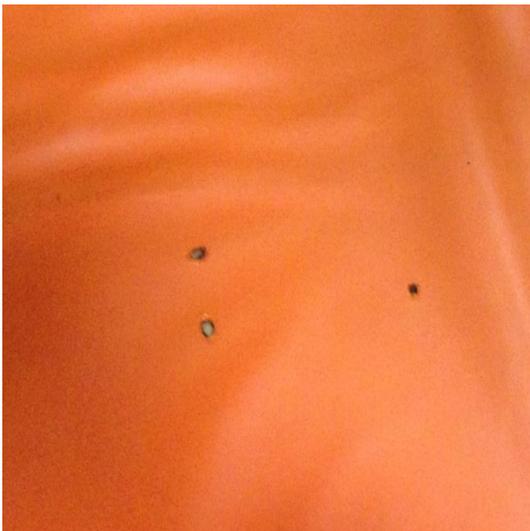
Stairs at the Schizophrenia Center



Waiting room at the Schizophrenia Center (1)



Waiting room at the Schizophrenia Center (2) Curtain of the waiting room



In relation to the effects of the qualitative study on myself and on participants, in my opinion complete smoking cessation or switching to low risk products such as an e-cigarette could be a solution to the above problems. This was one of my opinions prior to conducting this study. I think that this experience has made me so appreciative of qualitative research that it is now my intention to include a qualitative part in all my future research.

As a final point, I feel it is significant to point out the effects of the research process on the participants. For several participants, talking about cigarette dependence

created curiosity about possible solutions to quit or reduce smoking and the resources available to do so.

3.10 Conclusion

This qualitative study aimed to explore perspectives about traditional cigarettes compared with e-cigarettes, in addition to licenced cessation aids or e-cigarettes for smoking cessation or smoking reduction, in 30 participants with schizophrenia spectrum disorders, 50% motivated to quit and 50% unmotivated to quit. The findings could provide useful information and direction to augment the existing body of knowledge on smoking and vaping behaviour of smokers with schizophrenia spectrum disorders. They could also help to inform the study design of a single arm pilot study of smokers with schizophrenia not motivated to quit, the results potentially building on those of a previous study with first generation e-cigarettes also amongst smokers with schizophrenia not motivated to quit (Caponnetto et al., 2013d). In Italy the e-cigarette is not an approved cessation aid and Italian national guidelines recommend that if a person is motivated to quit smoking it is ethically correct to suggest licensed smoking cessation aids approved by the guidelines of the Italian ministry of health to quit smoking (OSSFAD, 2008). Also, if a treatment proves to be effective for those unmotivated to quit, it may be more likely to be equally or even more effective for those motivated to quit.

Findings from this qualitative study suggest that e-cigarettes may be an appealing smoking cessation or reduction strategy. A high-performing e-cigarette, as close to the traditional smoking experience as possible, easy to use and loaded with tobacco flavor similar to traditional cigarettes, may be helpful for this group of smokers. The next chapter describes a pilot study to test the feasibility of providing such an e-cigarette device to a group of smokers with schizophrenia spectrum disorders who are not motivated to quit smoking. Ideally, we would include motivated smokers but current ethics arrangements in Italy make this difficult because e-cigarettes are not licensed for smoking cessation.

CHAPTER 4: FEASIBILITY AND SINGLE ARM PILOT STUDY

4.1 Study title: Role of an electronic cigarette in smoking cessation or reduction for smokers with schizophrenia spectrum disorders: a feasibility and pilot single arm study

This chapter describes study procedures, methods, results and discussion of a feasibility, single arm pilot study conducted with 40 smokers with schizophrenia spectrum disorders. The limitations of this study and suggestions for future research are also included.

4.2 Background and objectives

At the start of this PhD research, there was almost no literature on e-cigarettes for smoking cessation for smokers with schizophrenia. There was just one small uncontrolled study conducted at CPCT by my own research team. This was the first study in the world investigating the effectiveness of e-cigarettes for smoking cessation/reduction in people with schizophrenia. This study found that 50% of smokers with schizophrenia who were provided with e-cigarettes for 12 weeks reduced their smoking by 50%, and 14% quit, with no increases in psychiatric symptoms (Caponnetto et al., 2013d). These preliminary findings are noteworthy, because none of the participants was initially seeking treatment for smoking. However, the study had several limitations including the absence of a control group, use of first-generation e-cigarettes model and a small sample (14 subjects).

Following this study, a protocol for a large three-armed RCT was prepared and published in the journal *Trials* in 2014 (Caponnetto et al., 2014). This outlined plans for a large multi-center study to assess changes in smoking behaviour in a group of 153 psychiatrically stable individuals with schizophrenia who would be offered second generation personal vaporizers to reduce the risk of their tobacco smoking. It was to be known as the SCARIS study.

The SCARIS study wasn't conducted (Caponnetto et al., 2014) because after a series of meetings with international experts in this field it became apparent that the study might be more complicated than originally envisaged. Colleagues raised

concerns about respondent burden (e.g., time, energy, and emotional expenditure by participants) given the number of questionnaires and measures to be used. There were also queries about the third arm of the trial, which was intended to include use of a plastic cigarette 'paipo', and it was suggested instead that e-cigarettes without nicotine could be used in the control group.

Before being able to proceed with the modified SCARIS study, reviewers and PhD supervisors suggested that more preliminary research was needed. This preliminary research is the focus of this chapter of the dissertation. The intention is that this early work will inform a future larger trial to be completed following the PhD and the protocol for this future trial is included in the Chapter 5. The study design was a single-arm pilot trial with the overall objective of evaluating the feasibility and preliminary effectiveness of e-cigarettes for smoking cessation. The design was informed by a conceptual framework for defining feasibility and pilot studies developed by Eldridge and colleagues. They argue that pilot studies are a subset of feasibility studies, rather than the two being mutually exclusive (Eldridge et al., 2016), and that single arm pilot studies (as in the current research) can still answer feasibility questions. Therefore, this single arm pilot study aimed to determine if and how the proposed intervention could be delivered in practice and how to proceed with testing the intervention in a future, larger study. Non-randomised single arm pilot studies are similar to randomised pilot studies except they do not include randomisation of study participants and they use a single arm. They are studies in which all or part of the intervention to be evaluated, and other processes to be undertaken in a future trial, are carried out (piloted) but without randomisation of participants (Eldridge et al., 2016).

In line with the objectives to pilot and assess feasibility, the study described in this chapter was designed to monitor possible modifications in the smoking behavior of a group of regular smokers with schizophrenia using a new generation e-cigarette (JUUL). The study also included assessments for body weight and users' perceptions of psychological reward, craving reduction, aversions, enjoyment and satisfaction. When this study began, JUUL e-cigarettes were not available in Italy and the EU. Other common devices used in Italy were considered for this study, like the Just Fog or the Blu cigalike, but we adopted the JUUL for its specific

characteristics of new generation e-cigarettes, previously explained in Chapter 2 (Section 2.2.2). Considering the lack of availability, the producers donated the product for use in the study, and also agreed to supply cartridges/pods for a further three months after the end of the pilot to participants who expressed a wish to continue using them.

4.3 Research questions

There are three main research questions for this single arm pilot study:

1. Will the participants quit smoking if they use this e-cigarette?
2. Will the participants reduce the number of cigarettes smoked if they use this e-cigarette?
3. Are the study procedures feasible, and are they acceptable to participants?

4.4 Methods

4.4.1 Study design

This was a 3-month single arm pilot study to observe cigarette use behaviour amongst a group of regular smokers with a schizophrenia spectrum disorder diagnosis who smoked traditional cigarettes, did not intend to reduce or quit smoking, and were invited to use an e-cigarette. We were interested to know if e-cigarette use is associated with cigarette smoking cessation. Cessation is defined as switching from traditional cigarettes to e-cigarettes. The e-cigarettes were offered to participants as an alternative to traditional cigarettes. Participants were not mandated to switch to e-cigarettes for the study. Other assessments included the extent of e-cigarette use, the stability of symptoms of schizophrenia, possible AEs associated with e-cigarette use, the effects of e-cigarette use on enjoyment of respiratory tract sensations, psychological reward and satisfaction, and the extent of acceptability of study procedures and e-cigarettes as substitutes for traditional cigarettes.

4.4.2 Study team

Although the research itself was conducted by the PhD candidate, the study benefited from the support and advice of colleagues in several institutions in addition to support from the PhD supervisors. Additional input was provided by Dr Jason Kim

from the Weill Cornell Medical College Clinical and Translational Science Center (CTSC) and Professor Jennifer DiPiazza from the Hunter Bellevue School of Nursing at Hunter College (HBSON) as well as Professor Riccardo Polosa from the University of Catania, Italy.

At the start of the study, it was intended that data would be collected in both Italy and the USA, with the Italian data to form part of the candidate's PhD. However, data collection did not proceed as planned in the USA. This was because the US researchers at the CTSC experienced several difficulties in enrolling the participants for this study that will be further explained in the discussion section of this chapter.

4.4.3 Ethics

Ethical approval for the single arm pilot study was obtained for both the Italian site and the proposed USA site from the relevant committees in both areas. These approvals along with the full protocol were also submitted to the University of Stirling ethics committee which approved the ethics application on 27 September 2017 (Appendix 6).

No separate funding was secured for the study. However, the e-cigarettes used in the study were donated by the manufacturer, an independent company (Pax Labs) that, at the time of the research, was not part-owned by the tobacco industry.

4.4.4 Participants

Forty participants were recruited between 29 September and 07 October, 2017 at CPCT, University of Catania, Italy.

4.4.5 Inclusion criteria

The participants were:

1. adult non-hospitalized daily smokers of 20 or more traditional CPD in order to compare the results with those of a previous study that enrolled heavy smokers (Evins et al., 2004) with schizophrenia spectrum disorders who smoked 20 or more traditional CPD (Caponnetto et al., 2013d).
2. aged 21 to 65 years.

3. not intending to reduce or quit smoking, firstly because Italian smoking cessation guidelines stipulate offering only approved therapies (varenicline, bupropion, NRT) and therefore it would be ethically incorrect to propose e-cigarettes for smoking cessation in Italy and secondly to compare the results with those of the same previous study (Caponnetto et al., 2013d) in which we enrolled, for the reason cited before, smokers not motivated to quit.
4. able to provide written informed consent, and read, write and communicate in Italian proficiently.
5. able to meet the criteria for a schizophrenia spectrum disorder diagnosis without evidence of current exacerbation of illness, defined as “no relapse to hospitalization within the last three months and no change antipsychotic treatment within the last month” (Mendrek, 2012).

In terms of this last inclusion criterion, a clinical psychologist or a psychiatrist not involved in the study made the diagnosis based on criteria from the DSM-V (APA, 2013), which was confirmed by electronic health records.

4.4.6 Exclusion criteria

Exclusion criteria were: 1) pregnancy, 2) breastfeeding, 3) myocardial infarction or angina pectoris within the past three months, 4) current poorly controlled asthma or COPD, 4) use of smokeless tobacco or any other tobacco products, 5) use of NRT or other smoking cessation therapies within the last three months.

4.4.7 Recruitment

A “Dear Provider Letter” was sent to physicians, psychiatrists and other health care providers to inform them about the study (Appendix 7). Flyers (Appendix 8) were posted within and outside of the CPCT, University of Catania, at the Policlinico Vittorio Emanuele. Participants were recruited from Catania outpatient psychiatric clinics by researchers of CPCT, University of Catania at the Policlinico Vittorio Emanuele. Clinicians from outpatient psychiatric clinics identified suitable participants and drew their attention to the study flyers.

Clinicians asked permission from potential participants to pass their contact details to the PhD student and an assisting clinical researcher (Appendix 9). If participants agreed, their details were passed on. The assisting clinical researcher then made

the first approach to eligible patients after they had been identified by health professionals in the clinics. Patients were given full study information and participant information sheets (PIS) (Appendix 10). At least 48 hours passed between participants receiving the PIS and a request to sign the consent form (Appendix 10) and start the BL visit with the PhD candidate.

4.4.8 Procedures

Participants were screened at the BL visit (study visit one), where eligible participants were invited to use a JUUL e-cigarette and were followed prospectively for 12 weeks. It was mentioned that the product was less harmful than traditional cigarettes and could be used as a cigarette substitute as much as they liked. Participants attended a total of four study visits at the smoking cessation clinic where the PhD candidate is employed: CPCT, Università di Catania at the Policlinico Vittorio Emanuele, Catania, Italy.

The BL visit and three follow-up visits at weeks four, eight, and 12 took place in the clinic. In between the BL and three study visits, participants were telephoned by the PhD candidate at weeks two, six, and 10 to confirm the next appointment and answer questions about product use.

The following were recorded at BL (study visit one): demographics, smoking history and pack-years, eCO, vital signs and body weight, scores on the FTCD (Fagerström, 2012) (Appendix 11) and SANS (Andreasen, 1983) and SAPS (Andreasen, 1984), two of the most widely used scales to measure symptoms of schizophrenia (van Erp et al., 2014) (Appendices 12 and 13).

To evaluate changes in symptoms of schizophrenia, the SANS and SAPS were repeated at each study visit by a qualified independent psychiatrist [Dr Roberta Auditore MD] not directly involved in the study and blinded to the study objectives. She used the REDCap system to administer the SANS and SAPS and data were inputted directly into the REDCap system. CO was measured by a portable device (Micro CO, Micro Medical Ltd, Kent, UK).

Participants were given a free e-cigarette kit containing one JUUL device with a charger and 5% nicotine cartridges/pods with instructions on how to charge, activate

and use the e-cigarette. A full four-week supply of pods equivalent to their current cigarette smoking behaviour, according to the manufacturer's guidelines, was given to each participant. Phone numbers were provided for both technical and medical assistance. In between study visits participants were asked to maintain a daily study diary recording product use, number of tobacco cigarettes smoked, and AEs.

To provide more information on the device used in the study, JUUL is an e-cigarette that has been created by Pax Labs. JUUL is a closed system ENDS product. The system consists of a device and closed pod. The pod contains 0.7 ml of e-liquid and up to 5% nicotine by weight. The e-liquid composition includes propylene glycol, glycerol, nicotine, benzoic acid, and flavouring. The product is charged via USB port. JUUL incorporates several key technological advances: JUUL is breath actuated and has no user modifiable settings; the battery (200 mah) is not removable, and the electronics incorporate battery regulation features; a unique temperature regulation system has been demonstrated to maintain coil and wick temperatures below 300 degrees Celsius under a range of operating conditions (cigarettes can exceed 1000 degrees Celsius).

At study visits two (week four), three (week eight), and four (week 12), participants were invited back for further assessments and to return unused study products, double check their study diary, and receive another four-week supply of pods/cartridges. At these visits the following data were recorded: number of traditional cigarettes smoked and pods/cartridges used daily since the last visit, CO, vital signs and body weight, and scores from the SANS and SAPS to assess symptoms of schizophrenia.

The Modified Cigarette Evaluation Questionnaire (mCEQ) (Cappellieri et al., 2007), adapted for e-cigarette (Steinberg et al., 2014), was used to examine acceptability (Appendix 14). For participants who used e-cigarettes, the mCEQ was used to assess effects of e-cigarette use on respiratory tract sensations, acceptability of e-cigarettes as substitutes for traditional cigarettes, psychological reward, and satisfaction. Previous studies have used this questionnaire for e-cigarettes (Steinberg et al., 2014; Carpenter et al., 2017; St. Helen et al., 2017). The mCEQ assesses five domains of smoking behavior (craving reduction, aversion,

psychological reward, satisfaction, and enjoyment) and its reliability and validity have been confirmed. Smoking satisfaction and psychological reward domains showed a Cronbach's alpha for internal consistency reliability > 0.70 , but < 0.70 for the aversion domain; test-retest reliability generally exceeded 0.70 on the three multi-item domains (smoking satisfaction, psychological reward, and aversion) and two single items (enjoyment of respiratory tract sensations and on craving reduction). The validity of this questionnaire is sustained by the analyses of three independent studies, with multi-item domains on satisfaction, psychological reward, and aversion, and single-item domains on enjoyment of respiratory tract sensations and craving reduction (Cappelleri et al., 2007).

The mCEQ was used with participants who reported having tried the e-cigarette at least once. It is a self-administered questionnaire that contains 12 items covering both the reinforcing and the aversive effects of smoking. Participants were asked to rate the extent to which the e-cigarette they used was satisfying, tasted good, made them dizzy, calmed them down, helped them concentrate, made them feel more awake, reduced appetite, made them nauseated, decreased irritability, produced enjoyable sensations in the throat and chest, immediately reduced craving for cigarettes and was enjoyable to smoke. The items were rated on a seven-point scale of 1 (not at all), 2 (very little), 3 (a little), 4 (moderately), 5 (a lot), 6 (quite a lot), and 7 (extremely). The mCEQ uses three multi-item domains (subscales) and two single items: "Smoking Satisfaction" (items 1, 2, plus item 12); "Psychological Reward" (items 4-8); "Aversion" (9, 10); "Enjoyment of Respiratory Tract Sensations" (item 3); and "Craving Reduction" (item 11). Higher scores indicate greater intensity of each smoking effect with, for example, greater satisfaction or psychological reward after vaping.

Participants who attended at least one study visit but missed the next study appointment were called by phone or sent an email (depending on participants' preferred method of communication). Limited behavioural support was provided as part of the intervention. In terms of behaviour change techniques, these were limited to behaviour substitution of traditional cigarettes with e-cigarettes and self-monitoring of traditional cigarette consumption through study diaries. Behaviour

substitution and self-monitoring are respectively coded as 8.2 and 2.3 in the Behavior Change Technique Taxonomy v1 (BCTTv1) (Michie et al., 2013).

4.4.9 Outcomes

Primary outcome

The primary outcome or endpoint of this study was the proportion of study participants who self-reported that they had stopped smoking (not even a puff) for the 30-day period prior to the week 12 study visit, along with a confirmatory CO reading of ≤ 10 ppm (Kendrick, 2010) as recommended by the Russell standard (West et al., 2005). These participants are referred to as “Quitters”.

Secondary outcomes

1. Smoking reduction was defined as a reduction in cigarette consumption by $\geq 50\%$ in the number of traditional cigarettes smoked per day compared with BL for the 30-day period prior to the week 12 study visit. CO levels were measured to verify smoking status and confirm a reduction compared with BL. These participants were referred to as “Reducers”. No change was defined as participants with a self-reported no change in traditional cigarette smoking consumption. Smokers who failed to meet the above criteria at the final week-12 follow-up visit were categorized as “Continuous Smokers”.
2. Adoption rate and adherence to product use as measured by 1) daily use of e-cigarettes during the 12 weeks of observation, and 2) $\geq 50\%$ e-cigarette use during the 12 weeks of observation. Participants were asked to keep track of the amount they used their e-cigarette using a study diary. The diary was reviewed with the participant by the researcher at each study visit. Participants who did not complete their diary in between study visits completed it during the study visit.
3. Feasibility and acceptability as measured by participants’ vital signs, weight and psychopathological changes, reported AEs and subjective effects of using the e-cigarette. Changes in vital signs (BP and HR) and weight were measured by difference between BL (visit1) and week 12 (visit 4). Changes in positive and negative symptoms of schizophrenia, were measured by the SANS and SAPS between BL (visit one) and week 12 (visit four).

Participants reported frequency and percent of AEs associated with e-cigarette use (Appendix 15). They were asked to keep track of any AEs they felt may be associated with e-cigarette using the study diary. The diary was reviewed with the participant by the researcher at each study visit. Subjective effects were assessed by mCEQ scoring that reported frequency and percent of participants reporting a) enjoyment of respiratory tract sensations, b) psychological reward, and c) satisfaction, amongst users of e-cigarettes. Acceptability of e-cigarettes as substitutes for traditional cigarettes was also assessed.

4.4.10 Statistical analysis

The primary outcome of this study was the proportion of study participants with self-reported complete cessation from traditional cigarette smoking (“Quitters”) at each study visit, along with confirmatory CO values of ≤ 10 ppm taken at each study visit. Because this was a single arm pilot study, a formal sample size calculation was not required. However, with approximately 40 participants in the study, a 95% CI for the proportion of study participants with self-reported complete cessation from traditional cigarette smoking at each study visit could be constructed to be within $\pm 17.6\%$ of the true proportion of “Quitters”. This first calculation, during protocol study design, using our previous work on the impact of e-cigarettes on smoking reduction and cessation in smokers with schizophrenia (Caponnetto et al., 2013d), which assumed that approximately 20% of participants would have achieved complete cessation from traditional cigarette smoking during the entire study period. Up to 40 participants were recruited at BL, as this study assumed a conservative attrition rate of 50%. Primary and secondary outcome measures were computed by including all enrolled participants assuming, on the basis of the intention-to-treat principle, that all individuals lost to follow-up would be classified as continuous smokers (West et al., 2005). Parametric and non-parametric data were expressed as mean (\pm SD) and median, interquartile range (IQR) respectively. The primary endpoint of the proportion of “Quitters” and CO values ≤ 10 ppm were reported descriptively.

The secondary endpoint of self-reported $\geq 50\%$ reduction in the number of traditional cigarettes smoked per day compared with BL for the 30-day period prior to the week 12 study visit and confirmatory CO reduction were reported descriptively. The

change in the number of cigarettes smoked per day for each visit compared with BL was assessed with the Wilcoxon signed rank test. No adjustments for multiple comparisons were performed given the exploratory (i.e., hypothesis-generating) nature of this study. The secondary outcomes of adoption and product use of a) self-reported daily e-cigarette use and b) $\geq 50\%$ e-cigarette use during 12 weeks of observation were reported descriptively.

Feasibility and acceptability measures (vital signs and weight, SAPS, SANS, AEs, SAEs, mCEQ) were reported descriptively. Descriptive statistics (including mean, standard deviation (SD), median, range, frequency, and percent) were calculated for patient demographics. All p-values were two-sided with statistical significance evaluated at the 0.05 alpha level. Analyses were performed in SPSS Version 23 (Statistical Package for Social Sciences Program, IBM Corp., Armonk, N.Y., USA).

4.5 Results

4.5.1 Participant characteristics

Fifty-six smokers with schizophrenia spectrum disorders responded to the study advert and were given the PIS. A total of 40 (M 26; F 14; mean (\pm SD) age of 48.3 (\pm 12.1) years) smokers (mean (\pm SD) pack/yrs of 45.4 (\pm 23.9) consented to participate and were included in the study (Table 4, Figure 4).

Figure 4. Study flowchart

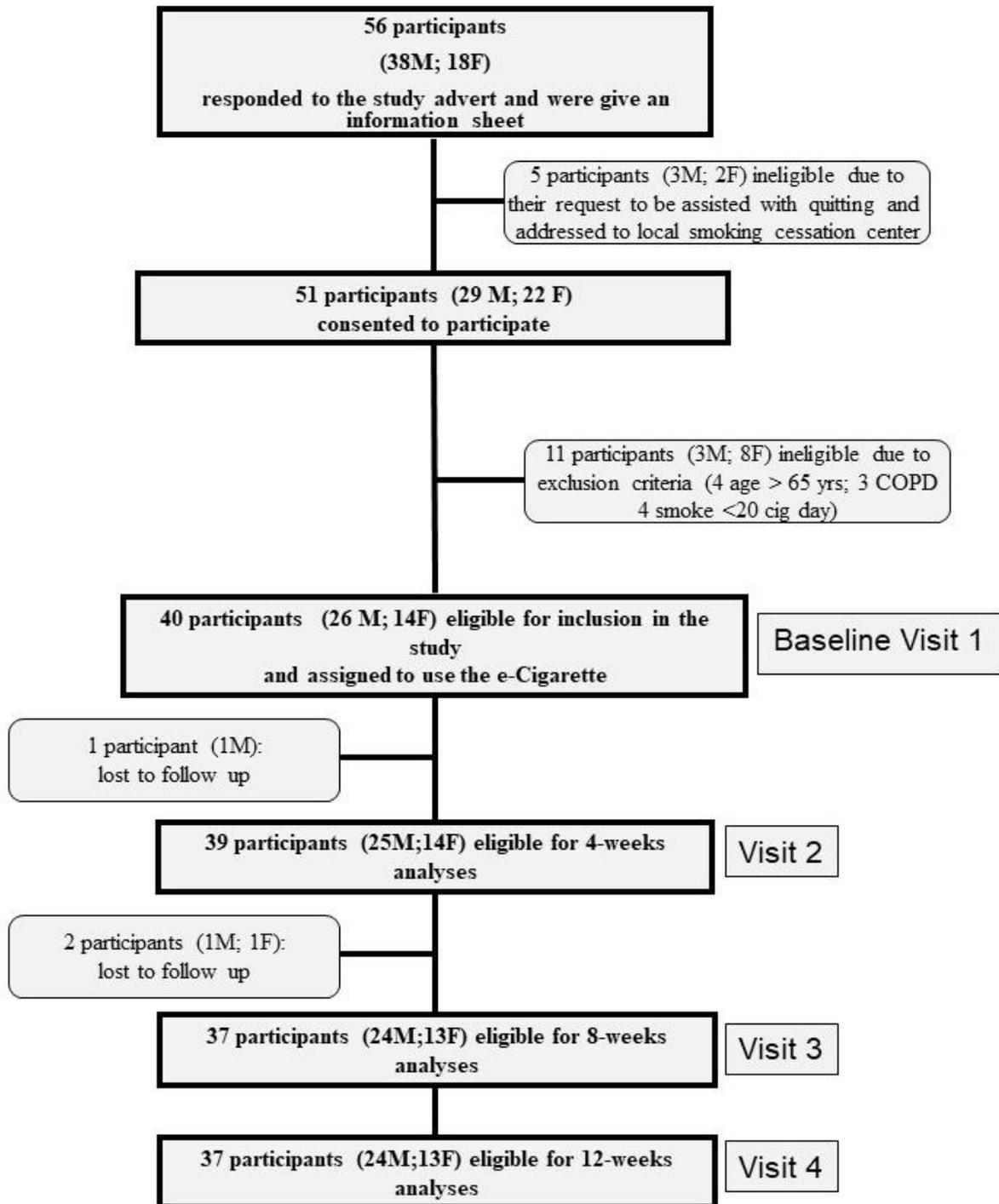


Table 4: Participants' characteristics

| Socio-demographic characteristics at baseline | n (%) |
|---|--------------|
| Gender | |
| Male | 26 (65) |
| Female | 14 (35) |
| Age: mean (SD) | 48.3 (12.1) |
| Age range | |
| 18-24 | 1 (2.5) |
| 25-44 | 13 (32.5) |
| 45-65 | 26 (65) |
| Education: n (%) | |
| Middle school | 22 (55) |
| High school | 17 (42.5) |
| University | 1 (2.5) |
| Ethnicity | |
| White Caucasian | 40 (100) |
| Asian | 0 (0) |
| African | 0 (0) |
| Smoking History | |
| CPD: mean (SD) | 28 (9) |
| Age of onset of smoking: mean (SD) | 15.4 (1.2) |
| Length of time smoking: mean (SD) | 33.5(12.2) |
| Pack/years: mean (SD) | 45.4 (23.9) |
| Smokers who have made previous cessation attempts: n (%) | 14 (35%) |
| Smokers who had previously used an e cigarette, either regularly or tried: n (%) | 12 (30%) |
| FTCD: mean (SD) | 8.3 (1.8) |
| Mental Health History and Status | |
| Age onset of schizophrenia spectrum disorders: mean (SD) | 21.9 (2.8) |
| SAPS at Baseline: mean (SD) | 42.9 (23.7) |
| SANS at Baseline: mean (SD) | 43.3 (21.7) |

The retention rate was high, with 37 (92.5%) participants completing all study visits and attending their final follow-up visit at week 12. A drop-out rate of 7.5% (3 of 40 participants) was observed. One participant chose not to participate after week two because he wanted to continue to smoke traditional cigarettes.

Two participants dropped out of the study after week four because they did not find the e-cigarette acceptable and reported that it caused them to cough. BL characteristics of those who were lost to follow-up were not significantly different from participants who completed the study. Recruitment and follow up was shown in the study flowchart (Figure 3).

4.5.2 Changes in smoking behaviour

Participants' tobacco consumption at BL and at 12 weeks is shown in Table 5.

Table 5. Participants' traditional cigarette consumption at baseline and at 12 weeks

| Event Name | N Obs | Variable | Mean | SD | Median |
|--|-------|-------------------|----------------|---------------|----------------|
| Baseline (visit 1) | 40 | Cigs number CO | 27.95 34.03 | 9.14 10.95 | 25.00 30.00 |
| Baseline (visit 1) Participants completed the study | 37 | Cigs number CO | 28.59 33.23 | 9.79 10.97 | 25.00 30.00 |
| Week 12 (visit 4) | 37 | Cigs number CO | 6.38 8.19 | 6.89 6.53 | 6.00 10.00 |

4.5.2.1 Smoking cessation

The Wilcoxon signed-rank test was used to test the difference in number of cigarettes smoked (self-report) between BL (visit 1) and 12 weeks follow up 12 (visit 4). The difference (decrease in cigarettes smoked) was significant at $<.001$. Sustained smoking abstinence at week-12 from BL (quitters) was defined as sustained self-reported abstinence from tobacco smoking (not even a puff) for the 30 days period prior to week-12 study visit. CO levels were measured to verify CO concentration of ≤ 10 ppm for the reducers/quitters as recommended by the Russell standard (West et al., 2005). There were 16/40 (40%) quitters in total, with 16/16 (100%) still using their electronic cigarette by the end of the study (Table 6, Figure 4).

4.5.2.2 Smoking reduction

Sustained 50% reduction in the number of CPD at week 12 was defined as sustained self-reported 50% reduction in the number of CPD compared with BL for the 30-day period prior to the week-12 study visit. CO levels were measured to verify smoking status and confirm a reduction compared with BL (Bolliger et al., 2000). A $\geq 50\%$ reduction in the number of traditional cigarettes smoked per day compared with BL for the 30-day period prior to the week-12 study visit and confirmatory CO reduction was found in 21/40 (52.5%) participants, with a median of 25 CPD at BL (IQR 20, 40) decreasing significantly to 10 CPD (IQR 8.5, 15) ($p < 0.001$) (Table 6).

For the whole sample, an overall, sustained 50% reduction or smoking abstinence was shown in 37/40 (92.5%) participants. (Figure 4). Taking the cohort of participants as whole (n = 40), an overall 75% reduction in median CPD use from 25 to six was observed by the end of the study (p < 0.001).

Table 6: Smoking behaviour outcomes

| Parameter | Baseline | 12 weeks | p-value‡ |
|--|---|---------------|----------|
| Quitters. 100% reduction in cigarette smoking (n=16) | Age 47.3(±9.7)† Pack Years 32.1(±14.5)† CPD 20 (20, 30)* | 0 (0, 0)* | <0,001 |
| Reducers. 50% reduction in cigarette smoking (n=21) | Age 49.3 (±14.1)† Pack Years 54.4 (±23.6)† CPD 25 (20,40)* | 10 (8.5, 15)* | <0.001 |

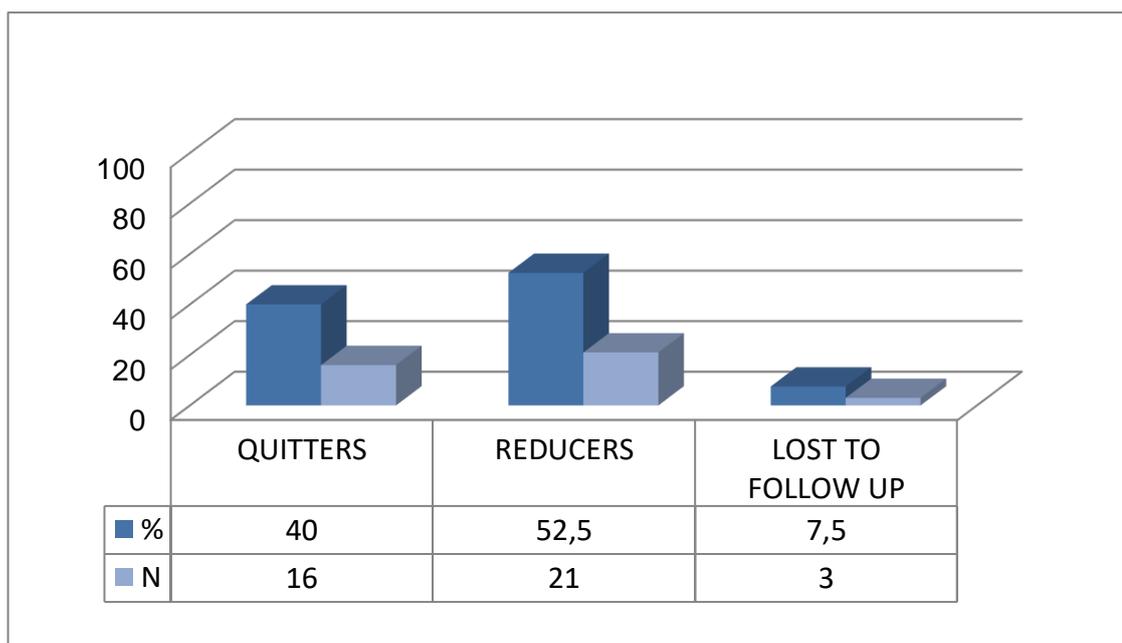
Abbreviations:

‡p-value within group Wilcoxon signed-rank test

† Parametric data expressed as mean (±SD)

*Non-parametric data expressed as median (IQR)

Figure 5. Changes in smoking behaviour at week 12



The Wilcoxon signed-rank test was used to test the difference in CO between BL visit and the final (12 week) visit. The observed difference (decrease in CO) was significant at < 0.001 .

4.5.3 Adoption rate and adherence to product use

All participants that completed the full schedule of visits ($n = 37$) reported using the e-cigarette each day over the 12 weeks, with a median (IQR) amount of e-cigarettes' cartridges/pods of one per day (1, 1) over the study duration.

4.5.4 Acceptability

This element of the study examined how smokers with schizophrenia spectrum disorders responded to the 12-week e-cigarette intervention. This research assessed participants' responses objectively and subjectively. Objective assessments included vital signs (BP and HR) and weight changes, any psychopathological exacerbations (assessed by SAPS and SANS); and any reported AEs from using the e-cigarette. Subjective effects were assessed by the mCEQ questions as described in the methods. Thirty-seven of 40 participants completed visit four at 12 weeks and, as described above, all of these participants were classified as quitters or reducers. Participants' vital signs, weight and psychopathological changes from BL to week 12 are shown in Table 7.

Table 7. Participants' vital signs, weights and psychopathological changes from baseline to week 12

| Event Name | N Obs | Variable | Mean | SD | Median |
|--------------------------|-------|---------------|--------|--------|--------|
| Baseline (Visit 1) | 40 | weight | 75.98 | 14.56 | 73.75 |
| | | heart_rate | 80.13 | 9.32 | 79.50 |
| | | bp_systolic | 133.48 | 9.91 | 135.00 |
| | | bp_diastolic | 76.73 | 7.20 | 80.00 |
| | | sans | 43.33 | 21.76 | 41.00 |
| | | saps | 42.90 | 23.74. | 36.50 |
| 12 weeks (Visit 4) | 37 | weight | 74.67 | 14.22 | 71.00 |
| | | heart_rate | 72.29 | 6.19 | 73.00 |
| | | bp_systolic | 121.41 | 8.59 | 123.00 |
| | | bp_diasstolic | 70.30 | 4.75 | 70.00 |
| | | sans | 44.89 | 21.33 | 44.00 |
| | | saps | 43.16 | 24.91 | 36.00 |

4.5.4.1 Vital signs (BP and HR) and weights

The Wilcoxon signed-rank test was used to test the difference in:

- systolic BP between BL (visit one) and 12-week follow up (visit four). The difference was significant at < 0.0001 .
- diastolic BP between BL (visit one) and 12-week follow up (visit four). The difference was significant at < 0.0001 .
- patient HR between BL (visit one) and 12-week follow up (visit 4 four). Again, the trends indicated a decrease. The difference between BL and visit four was significant at $p = < 0.0001$. The trend indicated that the systolic BP and HR decreased over the study period.
- patient weights between BL (visit one) and 12-week follow up (visit four). Again, the trends indicated a decrease. The difference between BL and visit four was significant at $p = 0.0052$.

4.5.4.2 Psychopathological changes during e-cigarette use

Positive and negative symptoms of schizophrenia were not significantly increased after using e-cigarettes from BL (visit one) to week 12 (visit four), suggesting absence of psychopathological exacerbation during the period when participants were e-cigarettes. The SANS difference between BL and visit 4 was not significant

at $p = 0.932$. The SAPS difference between BL and visit four was also not significant at $p = 0.809$.

4.5.4.3 Adverse events

Reported AEs amongst participants (Table 8) were dry cough (5.1 % at week four and 2,7% at week eight), headache (5,4% at week eight) and throat irritation (2.7% at week 12). These events were rare. Of note, typical withdrawal symptoms of smoking cessation were not reported (i.e. depression, anxiety, insomnia, irritability, hunger, constipation, weight gain). Moreover, there were no reported SAEs (i.e. events requiring unscheduled visit to the family practitioner or hospitalisation) during the study.

Table 8. Adverse events reported by participants

| AEs | Week four n/n (%) | Week eight n/n (%) | Week 12 n/n (%) |
|--------------------------|------------------------------|-------------------------------|----------------------------|
| Dry cough | 2/39 (5.1%) | 1/37 (2.7%) | 0/37 (0%) |
| Headache | 0/39 (0%) | 2/37 (5.4%) | 0/37 (0%) |
| Throat Irritation | 0/39 (0%) | 0/37 (0%) | 1/37 (2.7%) |

4.5.4.4 Subjective effects

The proportion and frequency of enjoyment of respiratory tract sensations, psychological reward and satisfaction amongst e-cigarettes users, and acceptability of e-cigarettes as substitutes for traditional cigarettes were assessed by mCEQ as illustrated below (Table 9).

Participants' responses to items related to the "smoking satisfaction" domain suggested that the majority of participants obtained satisfaction while using e-cigarettes. Response to items relating to the "psychological reward" domain suggested that the majority of participants obtained low levels of psychological reward associated with e-cigarette use. In relation to the "aversion" domain, the majority of participants reported no aversion to e-cigarette use.

Response to items related to the "enjoyment of respiratory tract sensations" domain suggested that the majority of participants reported moderate to significant

enjoyment (i.e obtaining a ‘throat hit’). In relation to the “craving reduction” domain, the majority of participants reported a moderate craving reduction associated with e-cigarette use (Table 9).

Table 9. Subjective effects of e-cigarettes: Participant responses to mCEQ questions n (%)

| "SMOKING SATISFACTION" | 1 not at all | 2 very little | 3 a little | 4 moderately | 5 a lot | 6 quite a lot | 7 extremely |
|---|-----------------|------------------|---------------|-----------------|--------------|------------------|----------------|
| Q1 "Was using your e-cigarette satisfying?" | 2 (1.8%) | 6 (5.3%) | 20 (17.7) | 16 (14.2%) | 46 (40.7) | 19 (16.8) | 4 (3.5%) |
| Q2 "Does the e-cigarette taste good?" | 4 (3.5%) | 4 (3.5%) | 7 (6.2%) | 28 (24.8%) | 58 (51.3) | 11 (9.7%) | 1 (0.9%) |
| Q12 "Do you enjoy using your e-cigarette?" | 1 (0.9%) | 2 (1.8%) | 12 (10.6) | 28 (24.8%) | 44 (38.9) | 15 (13.3) | 11 (9.7%) |
| "PSYCHOLOGICAL REWARD" | 1 not at all | 2 very little | 3 a little | 4 moderately | 5 a lot | 6 quite a lot | 7 extremely |
| Q4 "Does using your e-cigarette calm you down?" | 14 (12.4) | 10 (8.8%) | 38 (33.6) | 22 (19.5%) | 20 (17.7) | 8 (7.1%) | 1 (0.9%) |
| Q5 "Does using your e-cigarette make you feel more awake?" | 25 (22.1) | 20 (17.7) | 36 (31.9) | 18 (15.9%) | 13 (11.5) | 1 (0.9%) | 0 (0.0%) |
| Q6 "Did using your e-cigarette make you feel less irritable?" | 16 (14.2) | 18 (15.9) | 33 (29.2) | 26 (23.0%) | 12 (10.6) | 8 (7.1%) | 0 (0.0%) |
| Q7 "Did using your e-cigarette help you concentrate?" | 21 (18.6) | 13 (11.5) | 41 (36.3) | 16 (14.2%) | 17 (15.0) | 5 (4.4%) | 0 (0.0%) |
| Q8 "Does using your e-cigarette reduce your hunger for food?" | 33 (29.2) | 32 (28.3) | 22 (19.5) | 18 (15.9%) | 6 (5.3%) | 2 (1.8%) | 0 (0.0%) |
| "AVERSION" | 1 not at all | 2 very little | 3 a little | 4 moderately | 5 a lot | 6 quite a lot | 7 extremely |
| Q9 "Does using your e-cigarette make you dizzy?" | 92 (81.4) | 13 (11.5) | 5 (4.4%) | 0 (0.0%) | 3 (2.7%) | 0 (0.0%) | 0 (0.0%) |
| Q10 "Does using your e-cigarette make you nauseous?" | 83 (73.5) | 15 (13.3%) | 13 (11.5%) | 1 (0.9%) | 0 (0.0%) | 0 (0.0%) | 1 (0.9%) |

| “ENJOYMENT OF RESPIRATORY TRACT SENSATIONS” | 1 not at all | 2 very little | 3 a little | 4 moderately | 5 a lot | 6 quite a lot | 7 extremely |
|---|-----------------|------------------|---------------|-----------------|---------------|------------------|----------------|
| Q3 “Do you enjoy the sensations in your throat and chest?” | 11 (9.7%) | 2 (1.8%) | 14 (12.4%) | 34 (30.1%) | 32 (28.3%) | 14 (12.4%) | 6 (5.3%) |
| “CRAVING REDUCTION” | 1 not at all | 2 very little | 3 a little | 4 moderately | 5 a lot | 6 quite a lot | 7 extremely |
| Q11 “Does using your e-cigarette immediately reduce your craving for nicotine?” | 6 (5.3%) | 5 (4.4%) | 23 (20.4%) | 34 (30.1%) | 23 (20.4%) | 18 (15.9%) | 4 (3.5%) |

4.6 Discussion

Non-randomised or single arm pilot studies are an acceptable approach to testing the feasibility of interventions (Eldridge et al., 2016). These types of studies constitute research in which all or part of an intervention is evaluated and other study procedures are piloted for a future definitive trial, but without randomisation of participants. These studies are used to determine whether an intervention is appropriate for further testing; in other words, they enable researchers to assess whether or not the ideas and findings can be shaped to be relevant and sustainable. Performing this kind of study may be indicated when there are few previously published studies or existing data using a specific intervention technique. Commonly a number of issues are examined in these studies: initial efficacy, acceptability, demand, implementation, practicality and adaption (Eldridge et al., 2016; Bowen et al., 2009).

Given the very limited existing literature on the use of e-cigarettes for smoking reduction or cessation in adults with schizophrenia it was decided that a single arm pilot study would provide an achievable output as part of a PhD and could advance the field in terms of informing future research. For a single arm pilot study on this topic it was felt particularly important to assess demand (whether participants could be recruited and would consent to participate), test appropriate changes to smoking behaviour that could provide data to inform the design of a future trial, examine how feasible offering an e-cigarette was and whether participants with schizophrenia would use it, and also whether it was acceptable. More behavioural

support/counselling was not provided in this study because, although this may have been desirable the intention was to focus primarily on the e-cigarette elements of the intervention with a view to informing a large RCT. Also time, resource and staffing constraints for this small study, conducted as part of a PhD, also limited what could be provided in terms of behavioural support. However, it should be noted that participants did request more counselling in future similar studies.

Given this patient group it was also important to assess any changes in their mental health during the conduct of the study. This discussion section outlines:

- Outcomes in relation to the three research questions generated for the study
- The contribution of the PhD candidate
- Limitations
- Future research

4.6.1 Outcomes in relation to the research questions

This single arm pilot study had three main research questions as outlined above:

1. Will the participants quit smoking if they use this e-cigarette?
2. Will the participants reduce the number of cigarettes smoked if they use this e-cigarette?
3. Are the study procedures feasible, and are they acceptable to participants?

For research questions one and two, success rates in terms of complete smoking cessation or reduction of traditional cigarettes smoked at BL visit were observed. The majority of participants (92.5%) completed the study. At week 12, 16 of the 40 heavy smokers enrolled in study (40% of participants) completely stopped smoking by continuing to use the e-cigarette product provided. This proportion is higher than that found in previous studies with similar patient groups. For example, in the first ever study of e-cigarettes with patients with schizophrenia spectrum disorders (Caponnetto et al., 2013d), at week 52, two of 14 (14%) smokers of at least 20 CPD enrolled stopped smoking completely by continuing to use the product provided. In a study in the USA (Pratt et al., 2016), two of 19 (10.5%) participants with serious mental illness (schizophrenia, schizoaffective disorder, or bipolar disorder) switched completely to e-cigarettes without using combustible cigarettes at the four-week

assessment. In a more recent study conducted in UK by Hickling et al. (2018), with 50 smokers with severe mental illness (of which 42 (84%) had schizophrenia), by the end of the free e-cigarette phase at week six, 7% reported having stopped smoking traditional cigarettes.

A further 52% of the participants (21 of 40 (37%)), were able to sustain $\geq 50\%$ cigarette reduction by the end of the study by continuing to use the JUUL product. This finding is similar to that in previous studies where available. For example, in the Italian study mentioned above (Caponnetto et al., 2013d), at week 52, seven of 14 (50%) smokers were able to sustain $\geq 50\%$ cigarette reduction by the end of the study and the same measure of CO showed a significant decrease. The USA study conducted reported a 65% reduction in cigarette use in their participants (Pratt et al. 2016). In the recent UK study (Hickling et al., 2018), by the end of the free e-cigarette phase 37% of smokers had reduced the number of traditional CPD by $\geq 50\%$. These preliminary findings are promising in view of the fact that all smokers in the research were, by eligibility criteria, not motivated to quit smoking. Moreover, though it is not directly comparable with standard smoking cessation and/or reduction studies because of its design, success rates in the present study are not only similar to those obtained with approved pharmaceutical products for the treatment of nicotine addiction (Bennet et al., 2013; Peckham et al., 2017), but also greater than those for first generation and second generation e-cigarettes with similar patient groups (Caponnetto et al., 2013d; Pratt et al., 2016; Hickling et al., 2018).

This study showed that use of a new generation e-cigarette in heavy smokers not motivated to quit substantially decreased cigarette consumption without causing significant side effects. Although not specifically measured in this study, nicotine absorption using new-generation devices has been shown to be consistently superior compared with the first e-cigarette generation (Dawkins & Corcoran, 2014; Farsalinos et al., 2014a), which may form part of the explanation for higher quit rates than in studies using earlier generation devices. Considering its pharmacokinetic profile is similar to that of traditional cigarettes (Brown & Xing., 2015; Lawler., 2018) the e-cigarette used in this study may have provided a more 'cigarette-like' experience which may have promoted switching.

In terms of research question three, the study procedures appeared acceptable to participants. This is evidenced by the high retention rate. Given that few problems were experienced in conducting the research, the study procedures were also feasible. Although the study was small in size, it progressed well and this provides some confidence that the approach used here could inform a protocol for a larger trial (see Chapter 5). There is also evidence of feasibility and acceptability in terms of the short-term markers of physical and mental health assessed during the study. Participants showed significant improvements in BP and HR without weight gain, SAEs or psychopathological exacerbation. Other studies suggest that positive and negative symptoms of schizophrenia are not increased in patients using nicotine patches (Dalack et al., 1999; Dalack & Meador-Woodruff, 1999) bupropion (Evins et al., 2001) or early generation e-cigarettes (Caponnetto et al., 2013d). Specifically, in Caponnetto et al. (2013d), the same measures of positive and negative symptoms of schizophrenia (SAPS and SANS scales) were used without showing exacerbation of psychotic symptoms during the study. Some further evidence of acceptability relates to satisfaction with the performance of the e-cigarette used in the current research. Compared with the first pilot study conducted with 14 smokers with schizophrenia, which used a first-generation e-cigarette, in this study it was possible to observe improved product acceptance in terms of technological advancement, reliability of the product and the fact that participants remained in the study and continued to use the device. This is in marked contrast to the 2013 study in Italy in which the PhD candidate was involved. In that 2013 study, the patients used a five-piece product that was complicated to use, vape and recharge; with batteries, rechargers and atomizing devices that were frequently broken and of low durability; and with cartridges that often leaked liquid into the mouth and needed frequent changing because the manufacturer recommended a certain number of filters to be used per day.

In contrast, the e-cigarette used in this single arm pilot study is more advanced. For example, it is designed to avoid the “dry puff” phenomenon (Jensen, 2015), is breath actuated, and has no user modifiable settings. In addition, the battery is not removable, the electronics incorporate battery regulation features, and it has a unique temperature regulation system that has been demonstrated to maintain coil and wick temperatures below 300 degrees Celsius under a range of operating

conditions. Only three participants in the current study requested a new battery, and the single cartridge-pods per day were easy to use. The appearance of the product is also an improvement on the first generation “cigalike” used in the 2013 study (Figure 6).

Figure 6. First generation e-cigarette versus JUUL e-cigarette



The high level of satisfaction with the product under investigation is substantiated by the notion that 37 out of the 37 who attended the last study visit were still using their e-cigarette. This, together with the high retention rate and elevated rating in satisfaction scores, indicates that the quality and attractiveness of the study product may have played a vital role in attaining success rates. It is also interesting that other smokers who came into contact with the study participants, including some relatives and caregivers, a psychiatrist, several nurses and a psychologist, asked the study team where they could buy the product to quit or reduce their own cigarette smoking.

4.6.2 Contribution of the PhD candidate

The idea for this small trial was developed by the PhD candidate following the earlier work of our team in Italy. The trial was set up as a core part of the PhD and was intended from the beginning to form part of my thesis. Although this small trial should have enrolled 40 participants by a team in two countries (USA and Italy), as

discussed above the USA Center at NY Cornell University and City University of New York enrolled only one participant who immediately dropped out. Due to this and other challenges facing the US collaborators at the time, it was decided in discussion with the PhD supervisors to drop the US site. As a result, 40 participants were recruited in Italy only and the PhD candidate was responsible for all key aspects of the research.

In terms of the conduct of the final study, the PhD candidate developed the study concept and protocol design, was involved in recruiting participants, and was responsible for data collection and interpretation and for drafting and revising this chapter. The PhD candidate conducted the data analysis with assistance from a more senior statistician. A clinical research fellow assisted with recruiting participants and a psychiatrist was involved for SAPS and SANS assessments and their scoring.

4.6.3 Limitations

There were several limitations in this study. First, this was an uncontrolled study and the lack of a control group limits the internal validity and external validity of the findings. Confounding is usually a major threat to the validity of most associations based on uncontrolled data. Thus, the need for a future RCT, which is discussed in Chapter 5.

Secondly, the study involved exclusively heavy smokers (Evins et al. 2004) who smoked at least 20 CPD and cannot therefore be assumed to apply to all smokers with schizophrenia.

Thirdly, other characteristics of the sample and of the e-cigarette used limit the generalization of the findings: because of its unusual design (smokers not willing to quit) this was not an ordinary cessation study and therefore direct comparison with other smoking cessation studies involving smokers motivated to quit cannot be made; direct comparison with other smoking cessation studies using different e-cigarettes products cannot be made; all participants were outpatients and the findings reported from urban Sicilian residents in this study may not be valid for other population samples.

Lastly, because only a single nicotine strength (i.e. 5%) and a single aroma (i.e. tobacco flavour) were investigated in this study, it is possible that the study failed to provide options that could have increased cessation rates. Other research has suggested that unrestricted access to a wider selection of e-liquid nicotine strengths and flavours can play an important role in the attractiveness and success rates of these products (Farsalinos et al., 2014b).

4.6.4 Future research

Preliminary positive results from this single arm pilot study suggest that this intervention could be tested in an RCT. It will be important to discard or modify those interventions that do not seem to be feasible as a result of data collected during this early stage study.

Considering a future RCT, this programme could be implemented, extending further use of e-cigarette pods/cartridges for a further three months and with a follow up of one year. In addition to this programme, a specific brief smoking cessation counselling intervention could be added to help smokers first to switch to the e-cigarette and then to progressively become totally smoke and vape free. We could propose interventions with groups of smokers and the possibility of proposing this treatment in more centers where there are smokers affected by schizophrenia spectrum disorders (for example hospitals or departments of psychiatry, mental health units located in prisons). A future RCT could also include a study site in another country, such as the USA, to improve generalizability.

Other considerations are relevant to future research and were identified during this single arm pilot study. A problem that was encountered was the long duration of the data collection visits due to the long administration of SAPS and SANS at each visit. In anticipation of an RCT, rather than carrying out these assessments at each visit, they could be carried out every three months. In addition, many participants asked if there was a chance to have the electronic cigarettes for another three months and more counselling to quit smoking. Both of these elements could be incorporated into a future RCT.

Considering that smokers with schizophrenic spectrum disorders are heavy smokers, we included smokers who smoked at least 20 CPD and we used a latest generation model e-cigarette with a pharmacokinetic profile similar to traditional cigarettes, which was easy to use and had good technological performance and reliability to avoid unnecessary stress to the participants. A future RCT could employ the same or similar device. With a view to extending and proposing this model of intervention or in order to conduct an RCT for healthy participants or participants with other pathologies, it would be necessary to include people who smoke from 10 CPD and use cartridges/pods with lower nicotine levels, (e.g., allowing a maximum of 1.8% cartridge/pod nicotine levels in Europe). Any future studies conducted with healthy smokers could adapt specific diagnostic questionnaire tools depending on the disease group such as diabetes, COPD, alcohol or other substances dependence. Finally, a specific measure of possible dependence on e-cigarettes should be made at each follow up visit.

4.7 Conclusion

This study aimed to conduct preliminary research to begin to determine the effectiveness of an innovative smoking cessation intervention with an underserved population. The results provide useful information and direction to augment the existing body of knowledge on smoking cessation for people with schizophrenia spectrum disorders. If a future RCT is conducted and is successful, the findings could inform the roll-out of programmes or interventions to help reduce the number of people with schizophrenia who smoke.

CHAPTER 5: ROLE OF AN ELECTRONIC CIGARETTE IN SMOKING CESSATION OR REDUCTION FOR SMOKERS WITH SCHIZOPHRENIA SPECTRUM DISORDERS: A PROTOCOL FOR A LARGE MULTICENTER RANDOMISED CONTROLLED TRIAL

This chapter includes a formal protocol for a future RCT of e-cigarettes for smoking cessation or reduction in smokers with schizophrenia. The protocol was developed following the earlier stages of the PhD including the qualitative research included in Chapter 3 and the single arm pilot study included in Chapter 4.

The findings of both the qualitative research and the pilot study helped inform the protocol for future research. The relationship between key findings from each and how these findings influenced particular elements of the protocol is set out below in Table 10.

Table 10: How key elements of the qualitative and single arm pilot study informed the protocol for a future RCT

| QUALITATIVE STUDY FINDINGS | INFLUENCE ON RCT PROTOCOL |
|--|---|
| Compared with the motivated participants, participants who were not motivated to stop smoking considered the taste of traditional cigarettes to be an important part of their smoking experience and they preferred particular brands over others. | E-cigarette cartridges/pods with tobacco flavour, similar to traditional cigarettes, were used in the single arm pilot study and will also be used in a future RCT. |
| The majority of participants in both groups said they either did not like the taste of e-cigarettes or preferred the taste of traditional cigarettes. | As above, the selection of tobacco flavoured e-liquids seeks to address this finding. |
| Participants reported that they felt that using an e-cigarette was much more complicated than smoking traditional cigarettes. | The device used in the single arm pilot study (JUUL) is arguably one of the easiest to use on the market and the future RCT would also propose to use JUUL. |

| | |
|---|--|
| <p>All participants were aware that smoking traditional cigarettes causes several diseases but expressed different opinions about the potential impact of e-cigarettes on their physical health.</p> | <p>In order to examine perceptions of e-cigarette use on participants' physical health, two questions extracted from the interview used for the qualitative study will be included in follow-up questions to participants at weeks 12 and 24.</p> |
| <p>Participants reported that smoking traditional cigarettes had a positive effect on their mental health, either helping them feel less anxious and depressed or relieving stress. None of the participants mentioned a similar effect from e-cigarettes (amongst those who had used them and were interviewed).</p> | <p>For this reason, a high-performing electronic cigarette has been chosen for this trial to try and get as close to the smoking experience as possible. In addition, to examine the potential effect of e-cigarette use on participants' mental health, two questions extracted from the interview used for the qualitative study will be included in follow up questions to participants at week 12 and 24.</p> |
| <p>The qualitative results indicate that the intervention needs to improve awareness of licensed stop-smoking aids (particularly varenicline and bupropion) in this group of smokers.</p> | <p>Participants will have a screening visit, during which they will be informed about licensed smoking cessation aids in addition to the trial arrangements.</p> |
| <p>About half of participants in the sample reported interest in using e-cigarettes to quit or reduce smoking. Of these 16 participants, 12 were from the motivated group and four were from the not motivated group.</p> | <p>Ideally, we would include motivated smokers in the RCT but current ethics arrangements in Italy make this difficult (unlike in the UK where the Medicines and Healthcare products Regulatory Agency has taken a more permissive view) because e-cigarettes are not licensed for smoking cessation. Thus, in the future RCT we propose to include only smokers not motivated to quit because we will not easily get ethical approval for a new Italian trial using e-cigarettes for smokers motivated to quit.</p> |
| <p>SINGLE ARM PILOT STUDY FINDINGS</p> | <p>INFLUENCE ON RCT PROTOCOL</p> |
| <p>At week 12, there were 16/40 (40%) quitters in total. In addition, a sustained 50% reduction in the number of CPD was found in 21/40 (52.5%) of participants.</p> | <p>These are promising short-term results, but 12 weeks is not an outcome commonly used in RCTs and is likely to be of insufficient duration. Thus, for a future RCT the primary outcome should be fixed at week 24. The cartridges/pods will be dispensed for 24 weeks. Also 24 weeks equates to a 6-month follow up, which would allow a future RCT to be included in Cochrane reviews.</p> |

| | |
|--|---|
| <p>At week 12, the cessation and reduction rates, respectively 40% and 52%, were achieved by using a nicotine content of 5%.</p> | <p>These are promising cessation and reduction rates, but it's important to consider the cessation and reduction rates that could be archived by using the dosages allowed within the European Union and at the same time check the effect of the only e-cigarette factor in the absence of nicotine level impact. For these reasons a three-arm study with 5%, 1.7% and 0% nicotine has been designed.</p> |
| <p>The pilot study found that the study procedures (including the majority of the data collection instruments used) were acceptable to the patients and the e-cigarette device used was also acceptable.</p> <p>One exception to this was the burdensome frequency with which the SAPS and SANS data were collected.</p> | <p>Given the high degree of acceptability, the same measures and same device could be used in an RCT for comparison. However, a problem that was encountered was the long duration of the data collection visits due to the administration of SAPS and SANS at each visit. Consequently, SAPS and SANS data will only be collected every three months.</p> |
| <p>Many participants in the single arm pilot study asked to keep the e-cigarette for another three months and receive more counselling to quit smoking.</p> | <p>Both of these elements are incorporated in the RCT protocol. This also relates to the cost concern raised in the qualitative research. Longer-term provision of free support may enhance longer-term abstinence from smoking.</p> |

The overall aim of this thesis was to develop an intervention to create a study protocol for an RCT on the role of e-cigarettes in smoking cessation or reduction for smokers with schizophrenia spectrum disorders. This chapter aims to address this aim directly, and the format of the chapter is the same as would be included in a formal protocol paper for submission to a journal.

This will be a large trial focusing on effectiveness, safety and cost-effectiveness. Part of the structured interview used for the qualitative study (Chapter 3) will be included in this RCT. A full process evaluation with an in-depth qualitative research element could be added but would require more funding and plans, which could be developed following the PhD and once a suitable funder had been identified.

5.1 Title and summary

The title for the full protocol will be “New generation electronic cigarettes in smoking cessation or reduction for smokers with schizophrenia spectrum disorders (SCARIS 1.0): Study protocol for a multicenter randomised control trial”.

In summary, the protocol outlines the plan for an RCT investigating the effectiveness, safety and cost effectiveness of e-cigarettes. The intended study is a double-blind, placebo-controlled, randomised clinical trial designed to assess the effectiveness, safety and cost effectiveness of 5% nicotine new generation e-cigarettes in comparison with 1.7% nicotine new generation e-cigarettes and 0% nicotine new generation e-cigarettes (placebo) for smoking cessation or reduction.

The duration of active treatment will be 24 weeks. The primary endpoint of this study will be the proportion of study participants who self-report that they have stopped smoking (not even a puff) from the week-9 to the week-24 study visit, along with confirmatory CO readings of ≤ 10 ppm. These participants will be referred to as “Quitters”.

The differences of continuous variables between the three groups will be evaluated with the Kruskal-Wallis Test, followed by the Dunn multiple comparison test. The differences between the three groups for normally distributed data will be evaluated with the one-way ANOVA test, followed by the Newman-Keuls multiple comparison test. The normality of the distribution will be evaluated with the Kolmogorov-Smirnov test. Any correlations between the variables under evaluation will be assessed by Spearman r correlation. To compare qualitative data measured on a nominal scale, the Chi-square test will be used.

Objective: The primary objective is a comparison of 5% nicotine to 1.7% and 0% nicotine new generation e-cigarettes for smoking cessation efficacy after 24 weeks of treatment.

5.2 Methods

5.2.1 Trial design

The study will be a double-blind, three-arm parallel group, randomised controlled clinical trial designed to assess the efficacy and safety of e-cigarettes with 5% nicotine, e-cigarettes with 1.7% nicotine, and e-cigarettes with no nicotine.

Three arms of the study are needed because in the first arm we will see the effects of factor e-cigarette plus the 5% nicotine level, in the second arm the effects of the e-cigarette plus nicotine level (1.7%), and in the third arm we will see only the effect of single factor e-cigarette with its sensorial and hand-to-mouth experience in the absence of nicotine release. The Consolidated Standards of Reporting Trials (CONSORT) guidelines will be adhered to in the reporting of the trial.

5.2.2 Participants

The participants will be adult non-hospitalized daily smokers (10 or more traditional CPD, for at least the past five years, age 18 to 65 years) not motivated to quit smoking, meeting criteria for a schizophrenia spectrum disorder diagnosis without evidence of current exacerbation of illness, defined as no relapse to hospitalization within the last three months and no change in antipsychotic treatment within the last month (Mendrek, 2012).

A clinical psychologist or a psychiatrist not involved in the trial will make the diagnosis based on criteria from the DSM-V (APA, 2013), which will be confirmed by the electronic health record. The participant will be able to provide written informed consent and will be able to read, write and communicate in Italian proficiently. Motivation to quit will be assessed by the MTSS (Kotz et al., 2013). The MTSS has been chosen because it has been found to have a high correlation with other measures of current motivation to quit, and so it will provide a measure of motivation to quit smoking which would allow evaluation of all the most important aspects of motivation. This evaluation includes desire, intention and belief into one item with the expectation that this will guarantee the most cost-efficient assessment possible (Hummel et al., 2017).

Participants will be not eligible for the study in cases of pregnancy, breastfeeding, myocardial infarction or angina pectoris within the past three months, current poorly controlled asthma or COPD, and use of smokeless tobacco or any other tobacco products and/or use of NRT or other smoking cessation therapies within the past three months.

Settings: 300 regular smokers with schizophrenia will be recruited from three outpatient mental health clinics/psychiatric practices in Italy, with the support of their medical providers, inviting them to try e-cigarettes to reduce the risk of tobacco smoking. The participants will have visits in an outpatient clinic setting. Participants will attend their study visits at each study center at approximately the same time of day. With the exception of the BL study day, most visits will take approximately 10 to 15 minutes to complete. The flowcharts in Table 9 describe the procedures to be completed at each visit.

5.2.3 Ethics

This study must be conducted in compliance with Institutional Review Board/Independent Ethics Committee (IRB/IEC) informed consent regulations, and International Committee on Harmonization (ICH), GCP (Good Clinical Practice) Guidelines. An ethics proposal will be submitted to the relevant ethics committee in Italy, should the plan for the trial proceed following the PhD. In addition, all local regulatory requirements will be adhered to, in particular those which afford greater protection to the safety of the trial participants. This study will be conducted in general according to the Declaration of Helsinki and with local laws and regulations.

The investigator, or a person designated by the investigator, will explain the benefits and risks of participation in the study to each subject, the subject's legally acceptable representative or an impartial witness and obtain written informed consent prior to the subject entering the study (before initiation of protocol-specified procedures).

5.2.4 Interventions

The study will involve a total of six onsite visits, a screening visit, a BL visit and four visits (at weeks four, eight, 12 and 24) and three telephone contacts will be

scheduled during the treatment phase (at weeks two, six, and 10) (Figure 7). A total of 300 participants will be randomised in three study conditions (A, B, and C), 90 for each condition. Participants randomised in study group A will receive 24 weeks of JUUL e-cigarettes loaded with 5% nicotine level virginia tobacco aroma cartridges and smoking cessation counselling; those in study group B, will receive 24 weeks of JUUL e-cigarettes loaded with 1.7% nicotine level virginia tobacco aroma cartridges and smoking cessation counselling; participants in study group C will receive 24 weeks of JUUL e-cigarettes loaded with 0% nicotine level virginia tobacco aroma cartridges and smoking cessation counseling. These three arms of the study are set at different levels of nicotine to see the effect of different dosages on the consumption of traditional cigarettes.

Participants will receive 24 weeks of cartridges/pods because in the previous single arm pilot study most of the participants asked to have another three months of free products for these reasons: fear of traditional cigarette relapse, to try in the meantime to quit smoking traditional cigarettes, and to save money.

This model of e-cigarette was chosen because: it has a nicotine concentration comparable with a traditional cigarette; is easy to use; mimics the flavour, length, and mouth-feel of traditional cigarettes; is produced by a company (JUUL) not owned by a tobacco company; and does not require charging or re-filling. In addition, JUUL was successfully used in the single arm pilot study that informs this RCT protocol.

The JUUL is a cig-a-like that has been created by Pax Labs. JUUL is a closed system ENDS product. The system consists of a device and closed pod. The pod contains 0.7 ml of e-liquid and up to 5% nicotine by weight. The e-liquid composition includes propylene glycol, glycerol, nicotine, benzoic acid, and flavouring. The product is charged via USB port. JUUL was designed as an alternative to traditional cigarettes for adult smokers. Central to this is the ability to provide cigarette-like satisfaction via a pharmacokinetic profile similar to that of cigarettes (Brown & Xing., 2015; Lawler., 2018). JUUL incorporates several key technological advances: JUUL is breath actuated and has no user modifiable settings; the battery (200 mah) is not removable, and the electronics incorporate battery regulation features; JUUL has a

unique temperature regulation system that has been demonstrated to maintain coil and wick temperatures below 300 degrees Celsius under a range of operating conditions (cigarettes can exceed 1000 degrees Celsius). Notably, JUUL was designed to avoid the “dry puff” phenomenon (Jensen, 2015). The aerosol profile of JUUL’s flavors in stock have been characterized by independent third-party labs using validated analytical methods. Multiple categories of harmful and potentially harmful constituents from an FDA panel of 31 chemicals were found to be below the level of quantification, including carbonyls such as diacetyl and formaldehyde, volatile organic compounds such as benzene (also reported by Pankow, et al., 2017), and TSNAs such as NNN (nitrosonornicotine) and NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone).

The ‘smoking cessation counselling’ protocol for the trial will follow a Standard Treatment Programme (McEwen, 2014), and specialty training modules and briefings for practitioners who help smokers with mental health problems to quit (Robson & Potts, 2014; Robson & McEwen, 2018). The involved researchers will provide support in the form of CBT through one-to-one sessions. CBT has been developed on the basis of Pavlov’s, Skinner’s and Beck’s theories. CBT is an evidence-based treatment that aims to sustain smokers to achieve specific objectives, such as smoking cessation, through focussing on the current situation rather than the past (Guichenez et al., 2007).

Goal setting, review of behavioural goals, feedback on behaviour, self-monitoring, social support, information about health consequences, behaviour substitution, habit reversal, pros and cons, social reward, avoidance/reducing exposure to cues for the behavior, distraction, adding objects to the environment, and verbal persuasion about capability are the behaviour change techniques (BCTs) that will be used in this study. These BCTs are coded in Table 11 according to the Behavior Change Technique Taxonomy v1 (BCTTv1) (Michie et al., 2013).

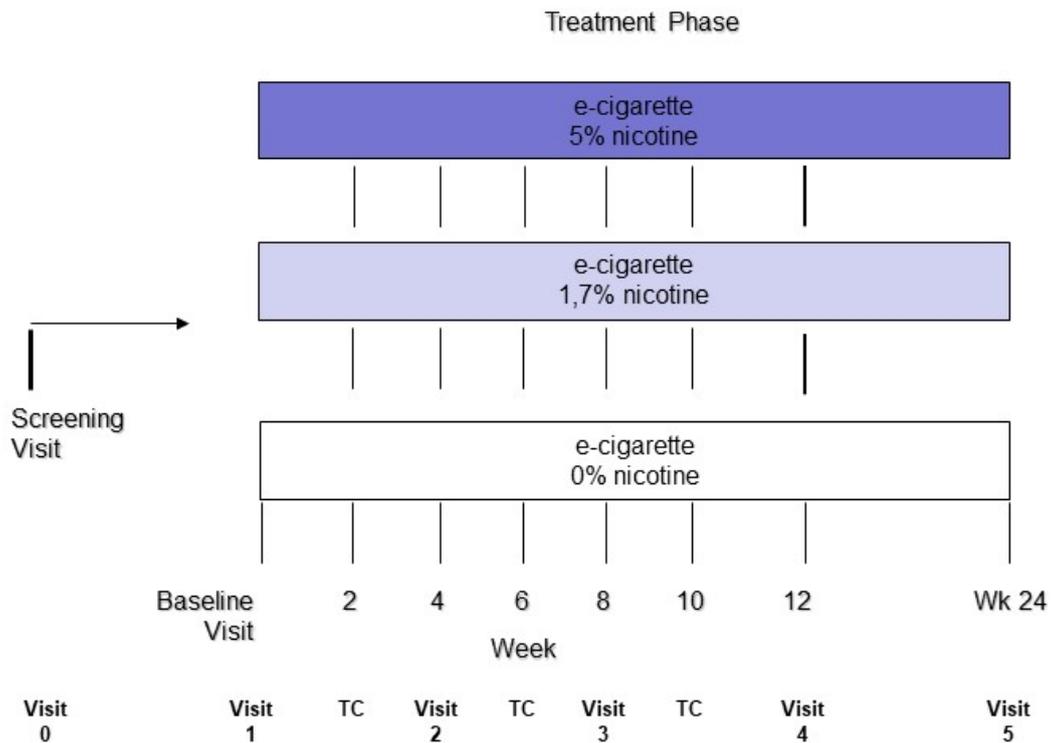
Table 11: Behaviour change techniques applied

| No. | BCTs applied |
|------------|---|
| 1.1 | Goal setting (behaviour) |
| 1.5 | Review behavioural goal(s) |
| 2.2 | Feedback on behaviour |
| 2.3 | Self-monitoring of behaviour |
| 3.3 | Social support (emotional) |
| 5.1 | Information about health consequences |
| 8.2 | Behaviour substitution |
| 8.4 | Habit reversal |
| 9.2 | Pros and Cons |
| 10.4 | Social Reward |
| 12.3 | Avoidance/reducing exposure to cues for the behaviour |
| 12.4 | Distraction |
| 12.5 | Adding objects to the environment |
| 15.1 | Verbal persuasion about capability |

Participants will be seen in a screening visit, during which eligibility criteria will be reviewed and informed consent will be obtained prior to any study procedures. Participants will also be informed about licensed smoking cessation aids, and if they choose to use one of these methods, they will be directed to the smoking cessation center closest to their residence.

The baseline visit will occur no less than three days and no more than two weeks after the screening visit.

Figure 7. Study diagram



5.2.5 Study procedures

The BL visit will be carried out within two weeks of the screening visit. At BL (study visit one), socio-demographic factors and detailed smoking history will be annotated and individual pack-years calculated, together with the ratings of positive and negative symptoms of schizophrenia, quality of life and neurocognitive functioning assessed by the SANS (Andreasen, 1983), the SAPS (Andreasen, 1984), the EQ VAS, (Rabin & De Charro, 2001) and BACS (Kefee RSE et al., 2004), respectively. SANS and SAPS have been chosen because, firstly, they are both used frequently in clinical and research settings and reliability and validity has been shown to be consistent in multiple cross-cultural settings (Andresen et al., 1991) and secondly, this enables comparison of the results with those obtained in the single arm pilot study. The EQ VAS is a valid and reliable measure in many disease areas (Wailoo et al., 2010) and is the most widely used generic patient-reported outcome questionnaire internationally (Devlin & Brooks, 2017). BACS has been chosen because it is designed to require about 30 minutes of testing time with minimal extra time for scoring and because it is designed to be administered easily by a variety of testers, including research nurse, clinical social workers, nurse clinicians, psychologists, psychiatrists and other mental health professionals.

Cigarette dependence will be measured with the FTCD (Fagerström, 2012) to evaluate if there will be any differences linked to the initial cigarette dependency level measured through this test.

The assessments at baseline and follow up will be carried out by a clinical psychologist or psychiatrist. Additionally, levels of CO in exhaled breath will be measured using a portable device (Micro CO, Micro Medical Ltd, Kent, UK). Vital signs (HR and BP, body weight) will also be recorded at BL. Participants will be asked not to smoke for at least 30 minutes prior to BL visit.

Participants will be given a free supply of e-cigarettes for 24 weeks (on average, a 4-week supply of e-cigarettes at a time) and instructed on how to use them. This visit will also cover general preparations for quitting and it should aim to enhance motivation and boost self-confidence throughout. Key trouble-shooting support will be provided and phone numbers will be supplied for medical assistance.

A study diary recording will be used to check the daily cigarette and pod/cartridge consumption and most common AEs related to the use of e-cigarettes (for example, dry cough, mouth irritation, throat irritation, headache, shortness of breath, nausea) and monitor/report symptoms of drug toxicity related to reducing or eliminating tobacco toxicity. Participants will be instructed to return every four weeks to obtain their four-weekly supply of e-cigarette pods/cartridges.

The BL (visit one) in brief is as follows: case report form (CRF) (physical examination, FTCD, EQ VAS, BACS, HR, BP, weight, CO, SAPS and SANS); randomisation into either study group A (e-cigarette 5% nicotine), B (e-cigarette 1.7% nicotine), or C (e-cigarette 0% nicotine); dispense four-week supply of nicotine 5% e-cigarette, nicotine 1.7% e-cigarette or no-nicotine e-cigarette (depending on the study-arm allocation); dispense four-week study diary; book for next appointment in four weeks (week four; study visit two).

At week four (study visit two), and week eight (study visit three), participants will a) receive the study diaries for the residual study periods; b) have their cigarette and

e-cigarette consumption recorded, c) have their CO levels and vital signs recorded; d) return their completed study diaries and used study products, e) be assessed, using the mCEQ (Cappelleri et al., 2007), for enjoyment of respiratory tract sensations, craving reduction for cigarettes, psychological reward, aversions, and satisfaction will be assessed. The mCEQ has been chosen firstly, to compare the results with those obtained in the single arm pilot study and, secondly, to obtain self-report measures in relation to behavioural preference of e-cigarettes varying in nicotine content. These visits will also cover strategies for avoiding cigarette smoking and should aim to enhance motivation and boost self-confidence throughout.

Week four (visit two) in brief will be as follows: collect four-week study diary; CRF (number of CPD, number of cartridges/day, CO, HR, BP, mCEQ); record cigarette and e-cigarette consumption; dispense four-week supply of nicotine 5% e-cigarette, nicotine 1.7% e-cigarette or no-nicotine e-cigarette (depending on the study-arm allocation); dispense next four-week study diary for AEs; book for next appointment in four weeks (week eight; study visit three).

Week eight (visit three) in brief will be as follows: collect four-week study diary; CRF (number of CPD, number of cartridges/day, CO, HR, BP, mCEQ); dispense four-week supply of nicotine 5% e-cigarette, nicotine 1.7% e-cigarette or no-nicotine e-cigarette (depending on the study-arm allocation); dispense next four-week study diary for AEs; book for next appointment in four weeks (week 12; study visit four).

At week 12 (study visit four), and week 24 (study visit five), participants will a) receive the study diaries for the residual study periods; b) have their cigarettes and e-cigarettes consumption recorded; c) have their CO levels and vital signs and weight recorded; d) return their completed study diaries and used study products; e) be assessed using the mCEQ (Cappelleri et al., 2007) for enjoyment of respiratory tract sensations, craving reduction for cigarettes, psychological reward, aversions, and satisfaction; f) be measured for cigarette dependence with the FTCD (Fagerström, K, 2012); g) be rated for positive and negative symptoms of schizophrenia, quality of life and neurocognitive functioning by the SANS and the SAPS (Andreasen, 1982), EQ VAS (Rabin & De Charro, 2001) and BACS (Kefee

RSE et al., 2004), respectively; and h) be measured for e-cigarette dependence with the Penn State [Electronic] Cigarette Dependence Index (Foulds J, et al., 2015). The last questionnaire has been chosen to evaluate whether or not the use of the products under investigation can determine dependence in these population.

These visits will also cover strategies for avoiding cigarette smoking and should aim to enhance motivation and boost self-confidence throughout. At the end of the week-24 study visit, no more products will be provided by the investigators. The study will be conducted where the products under investigation are available on the market online and in retail outlets. Smoking cessation counselling will be offered during all planned visits. After closing the study, participants will be directed to the smoking cessation center nearest to their place of residence.

Week 12 (visit four) in brief will be as follows: collect four-week study diary; CRF (number of CPD, number of cartridges/day; CO, HR, BP, weight; EQ VAS; SAPS, SANS; BACS; mCEQ; FTCD; Penn State [Electronic] Cigarette Dependence Index); brief structured interview about effects of smoking and/or vaping on mental and physical health; dispense 12-week supply of nicotine 5% e-cigarette, nicotine 1.7% e-cigarette or no-nicotine e-cigarette (depending on the study-arm allocation); book for next appointment in 12 weeks (week 24; study visit five).

Week 24 (visit five) in brief is as follows: collect 12-week study diary for AEs; CRF (number of CPD, number of cartridges/day; CO, HR, BP, weight; EQ VAS; SAPS, SANS; BACS; mCEQ; FTCD; Penn State [Electronic] Cigarette Dependence Index); brief structured interview about the effects of smoking and/or vaping on mental and physical health.

The early termination visit (ET; unscheduled visit) will involve: CRF (number of CPD; CO; HR; BP; weight; SAPS, SANS; BACS; EQ VAS; FTCD; Penn State [Electronic] Cigarette Dependence Index (Table 9).

5.2.6 Study Discontinuation

The proposed study will be stopped when required study numbers are achieved. Recruitment at a center may be stopped for reasons of low recruitment, protocol violation or inadequate data recording.

Table 12: Study Schedule/Flowchart

| PROCEDURE | | SCREENING VISIT 0 | BL VISIT 1 | WK4 VISIT 2 | WK8 VISIT 3 | WK12 VISIT 4 | WK24 VISIT 5 | ET |
|---------------------------------------|--|----------------------|------------------|-------------------|-------------------|--------------------|--------------------|----|
| Eligibility criteria (review) | | x | | | | | | |
| Informed consent | | | x | | | | | |
| Randomisation into either study group | | | x | | | | | |
| CRF | Socio-demographic factors | | x | x | | | | |
| | Smoking history | | x | x | | | | |
| | Number of CPD | | x | x | x | x | x | x |
| | Number of cartridges/day | | | x | x | x | x | |
| | Physical examination | | x | | | | | |
| | Vital signs – BP & HR | | x | x | x | x | x | x |
| | Weight - kg | | x | | | x | x | x |
| | AEs | | x | x | x | x | x | x |
| | FTCD | | x | | | x | x | |
| | Penn state [electronic] cigarette dependence index | | | | | x | x | |
| | EQ VAS, BACS, SAPS SANS | | x | | | x | x | x |
| | mCEQ | | | x | x | x | x | |

| | | | | | | | | |
|--|---|--|---|---|---|---|---|---|
| | Brief structured interview | | | | | X | X | X |
| | CO | | X | X | X | X | X | X |
| | Dispense study products and study diary | | X | X | X | X | X | |
| | Counselling | | X | X | X | X | X | |

5.2.7 Outcomes

The primary outcome for the trial will be continuous abstinence from smoking at week 24. Participants will be classified as ‘quitters’ if they are able to maintain complete abstinence from cigarette smoking from week nine through week 24 with end-expiratory exhaled CO measurements ≤ 10 ppm. This outcome was chosen, firstly, to verify the efficacy of the e-cigarette at different levels of nicotine as a tool for smoking cessation and for a significant period of time (24 weeks), in this category of smokers typically difficult to help to quit smoking traditional cigarettes, and secondly, because measuring the primary outcome at 24 weeks will also allow inclusion in the Cochrane reviews.

Secondary outcome measures will include:

- continuous abstinence rate from week nine through week 12;
- continuous reduction rate from week nine through week 12;
- continuous reduction rate from week nine through week 24;
- safety
- cost effectiveness
- change from baseline in results of SAPS, SANS, BACS, FTCD, Penn State [Electronic] Cigarette Dependence Index, and mCEQ

Safety will be assessed by measuring and recording AEs including symptoms thought to be related to tobacco smoking and e-cigarette use and to withdrawal from nicotine. These will be annotated at BL and at each subsequent study visit on the AE page of the study diary. Vital signs (BP, HR) and body weight will be also recorded to help inform an assessment of safety.

Cost effectiveness will be assessed by an embedded economic evaluation. This will be carried out in the form of an incremental cost-effectiveness analysis over the 12-month trial period. An experienced health economist will be included in the study team if the research proceeds as hoped, and any protocol developed for publication or for submission to a funder would include further details on the economic analysis provided by the health economist colleague. Intervention costs will be recorded by the research team and include e-cigarette costs, insurance cost, training costs, delivery costs within the trial, coordination and supervision costs and appropriate capital costs. An adapted Health Economic and Service Utilisation Questionnaire and case notes will be used to count and evaluate human resources use. Resource units will be calculated by multiplying quantities by the associated market costs or local average unit costs. Health-related quality of life will be assessed using EQ VAS (Rabin & De Charro, 2001). Health advantages will be transformed into quality-adjusted life years (QALYs), by obtaining the area under curve (Richardson & Manca, 2004). An incremental cost-effectiveness ratio (ICER) will be considered by linking variance in costs between groups and difference in QALYs between groups and related to the national willingness-to-pay threshold to determine cost-effectiveness.

5.2.8 Sample size

This will be a large RCT that will use the JUUL e-cigarette with different nicotine levels (5%, 1.7% and 0%) in smokers with schizophrenia spectrum disorders, the first of its kind; hence, no previous data are available for an accurate power calculation. The six-month continuous abstinence rates used in estimating this sample size were extracted from the single arm pilot study protocol. Since there was no basis for assessing the long-term quit rate in the single arm pilot study, the assumption has been made that the rates and relative differences for this endpoint would be at least as good as the continuous abstinence through week 24. In our single arm pilot study, reported in Chapter 4, we used JUUL e-cigarettes in 40 smokers with schizophrenia spectrum disorders, supplied with 5% nicotine cartridges/pods, and we reported a quit rate of 40% at three months in smokers not wishing to quit and with an observed attrition rate of 7.5%. Other previous research that is relevant was our first large long term RCT (Caponnetto et al., 2013c, conducted separately from and prior to the PhD), in which we used first generation

e-cigarettes in 300 smokers without schizophrenia spectrum disorders, experimenting with two different nicotine strengths compared with a non-nicotine choice, and we reported a quit rate respectively of 12%, 10% and 5% in arms with high, medium and no nicotine level and with an associated attrition rate respectively of 35%, 37% and 45%.

A sample size of 213 subjects will be aimed for in this RCT following any drop out. The sample size was calculated in line with the following parameters: effect size medium in smoking abstinence = 0.18; alpha = 0.05; power (1-β) = 0.80.

Considering that the drop out rate could be higher in the group without nicotine, we have assumed a drop-out rate of 30%; hence, a total sample size of 300 smokers at recruitment will be needed. The smokers will be randomised into the three arms of our study protocol (i.e., 100 smokers for each arm).

5.2.9 Randomisation

At BL, participants will be randomised into three separate study groups. The randomisation sequence will be computer generated by using blocks of 15 with an allocation ratio of 5:5:5 for each of the three study conditions (A, B, and C). Participants randomised in study group A will receive a 24-week supply of the e-cigarette with 5% of nicotine; those in study group B, a 24-week supply of the e-cigarette with 1.7% of nicotine; participants in study group C will receive a 24-week supply of the e-cigarette with 0% of nicotine. Blinding will be ensured by the identical external appearance of the e-cigarettes and cartridges. The hospital pharmacy will be in charge of randomisation and packaging cartridges. At the initiation of the study, staff at the study site will be instructed on the method for blind breaking. The method will be either a manual or electronic process. Blinding codes should only be broken in emergency situations for reasons of subject safety. When a blinding code is broken, the reason must be fully documented.

5.2.10 Statistical methods

Statistical analysis will be performed with SPSS 23.0 (IBM). Continuous variables will be described as mean and SD (for normally distributed variables), or median and IQR (for not normally distributed variables). Categorical variables will be

described with percentages and absolute frequencies. The differences in continuous variables between the three groups will be evaluated by the Kruskal-Wallis test followed by the Dunn multiple comparison test. The differences between the three groups for normally distributed data will be evaluated by one-way ANOVA followed by the Newman-Keuls multiple comparison test. The normality of the data distribution will be evaluated by means of the Kolmogorov-Smirnov test. Any correlation between the variables under evaluation will be assessed by Spearman r correlation. To analyze differences in frequency distribution of categorical variables we will use the Chi-square test with the Yates correction or the Fisher exact test. All statistical tests are two-tailed and are considered to be statistically significant at $P < 0.05$.

The consistency of effects for pre-specified subgroups will be assessed using tests for heterogeneity. Subgroups will be based on age, sex, education, and level of nicotine dependence.

Smokers who leave the study before its completion due to lack of efficacy or poor tolerability of the product under investigation will be subject to an ET and will be defined as continuous smokers. AEs, including symptoms thought to be related to tobacco smoking, e-cigarette use, and withdrawal from nicotine, will be annotated at each subsequent study visit to BL on the AE page of the study diary. The number and the percentage of subjects experiencing AEs, adverse reactions, SAEs and AEs leading to study withdrawal will be summarized by treatment group. AEs will also be summarized by system organ class and preferred term using the MedDRA dictionary.

A logistic regression model will be fitted to binary endpoints and will include treatment and center as independent variables. Subjects who discontinue the study are assumed to be smokers for the remainder of the study. In responder rates, those subjects will be represented in the denominator but not the numerator. For continuous endpoints, a linear model including treatment and center will be used as the underlying model.

5.2.11 Study plan

It is anticipated that it will take about three months to comply with all regulatory requirements (ethics committee review and approval). The study, from the enrollment to the study close out for all the patients at week 24 (follow-up), will have a total duration of 12 months.

The enrollment period will last about six months with the support of a multi-channel advertising method. This will include location-based advertising on social networks, advertising in local media, and information days organized within the city. It will take about five months for data cleaning; data analysis; writing the draft, interim, and final reports; manuscript writing; and submission of a results paper to a peer-reviewed journal.

Dissemination activities will be undertaken after the clinical study closes, that is, when all study visits have been completed by all the participants. The study results will be disseminated principally through peer reviewed academic publications and by way of dissemination events such as academic conferences. We will prioritise the use of open access channels in the course of dissemination activities.

5.2.12 Next steps

The study protocol, after adjustments following comments from the PhD examiners, and seeking additional external input on the health economics element, will be submitted to a peer reviewed scientific journal.

CHAPTER 6: DISCUSSION

In this concluding chapter, the key findings of the research conducted for this thesis are discussed.

The main aim of this thesis was to conduct preliminary research that would help inform the development of future research to assess the role of e-cigarettes in smoking cessation or reduction for smokers with schizophrenia spectrum disorders. The preliminary research was also intended to explore what would be acceptable and feasible for this target group and was underpinned by a robust theoretical basis. The final goal was to develop an intervention to reduce the risk of tobacco smoking, as a complementary tool to treat smokers with schizophrenia spectrum disorders. Specific objectives for the PhD were to: explore the perceptions of participants regarding e-cigarettes and licensed smoking cessation aids through a qualitative study; investigate the role of e-cigarettes on smoking cessation/reduction in smokers with schizophrenia through a prospective three-month single arm pilot study; and develop a protocol for a definitive trial to investigate the role of e-cigarettes on smoking cessation in smokers with schizophrenia in a large multisite RCT with longer term follow up.

Work towards this aim and these objectives was carried out using a mixed method approach based on a review of relevant literature, one qualitative study and one quantitative single arm pilot study.

First the contents of the thesis and main findings of the empirical work are summarized. Secondly, the findings of this empirical work are revisited and reflected upon in the context of the wider literature. These reflections relate firstly to the three research questions developed for the qualitative research outlined in Chapter 3 and secondly to the three research questions developed for the single arm pilot outlined in Chapter 4. How the findings address these questions is discussed in the context of the wider literature. In the remaining sections of this chapter the strengths and limitations of the research conducted as part of this thesis are examined, as are the implications for clinical practice and future research.

6.1 Summary of the research

Chapters 1 and 2 of this thesis reviewed the available literature in relation to: the epidemiology of tobacco smoking in people with schizophrenia; the relationship between smoking and mental health; harmful effects in patients with schizophrenia compared with the general population; the evidence base of the licensed smoking cessation treatments in the general population and in people with schizophrenia spectrum disorders; the concept of THR; and the description of e-cigarettes and relevant characteristics and potential application to improve health; and they also explored e-cigarettes for smokers with schizophrenia spectrum disorders.

Findings from the qualitative study reported in Chapter 3 suggested that smokers with schizophrenia spectrum disorders started to smoke for similar reasons to people without a mental health condition. In addition, they were aware of nicotine patches and nicotine gum as licensed smoking cessation aids, had never heard of varenicline and bupropion, and reported interest in using e-cigarettes to quit or reduce their consumption of traditional cigarettes.

Findings from the quantitative single arm pilot study reported in Chapter 4 suggested that the components of the intervention were feasible and acceptable to this group of smokers. Potential barriers and facilitators were identified which could inform future research, and important elements to assess in future studies were identified including: assessing improvements to BP and HR without weight gain; monitoring SAEs, and monitoring psychopathological exacerbation. The process of conducting the single arm pilot study and its outcomes directly informed plans for a future larger study which are outlined in Chapter 5. This consisted of a draft protocol for an RCT of e-cigarettes for smoking cessation or reduction in smokers with schizophrenia.

6.2 Perspectives on smoking and e-cigarettes amongst people with schizophrenia spectrum disorders

This section revisits the three research questions developed for the qualitative study included in the thesis (Chapter 3, Section 3.4) and considers these in the light of relevant literature.

Question 1: *How do participants perceive traditional cigarettes compared with e-cigarettes?*

The qualitative study found (Chapter 3) that around one in three study participants considered traditional cigarettes to be more expensive than e-cigarettes or with an equivalent cost. Similar proportions considered traditional cigarettes to be less expensive than e-cigarettes and were uninformed about e-cigarettes costs. Only one other previous study has explored these issues in smokers with schizophrenia spectrum disorders, and 32% of participants in that study (a similar proportion to the current results) expressed concern about the cost of e-cigarettes as a deterrent to use (Miller et al., 2017).

The qualitative study participants reported preferences for the taste, satisfaction and enjoyment of their own traditional cigarettes compared with e-cigarettes. All smokers were aware that smoking cigarettes causes several illnesses, but those unmotivated to stop were ambivalent about some of the health consequences. Members of the group that was motivated to quit, in contrast, were particularly concerned that smoking cigarettes might damage their health.

Smoking cigarettes for participants in the qualitative study was seen as a way to structure time and occupy the day. In a previous qualitative study conducted with psychiatric clients living in the community, including smokers with schizophrenia, participants reported smoking cigarettes gave them a sense of identity, and that traditional cigarettes were reported as the marker that kept all elements of their lives in control: they regarded smoking as a symbol of control (Lawn et al., 2002).

When comparing possible experiences from using an e-cigarette compared with smoking (other than health factors), views were similar amongst those interviewed. All participants described smoking as helpful, relaxing and 'a friend' available to cope with negative sensations that occurred as a result of their mental health condition. None of the participants from either group mentioned a similar effect from e-cigarettes. Another aspect they emphasized was the complexity of using e-cigarettes compared with traditional cigarettes and the effort required. These findings are similar to previous studies, including qualitative research, which has found that smoking traditional cigarettes offers a sense of control of mental health

symptoms in smokers with serious mental illness (Lawn et al., 2002; Barr et al., 2008b).

Although smokers believe that smoking offers mental health benefits there is also a strong association between smoking and poor mental health (Taylor et al., 2014). Smoking and disturbed mental health results in smoking to regulate feelings such as low mood and anxiety (Khantzian, 1997). Smokers with mental health diseases might be less likely to stop if they believed their mental health would suffer, and health professionals are often reluctant to treat this target group of smokers because they believe that this might be detrimental to their mental health (Johnson et al., 2010; Ratschen et al., 2009).

In terms of vaping and health risks, most participants unmotivated to quit were not aware of the possible impact of vaping on their health, particularly in relation to risks relative to smoking. Amongst those motivated to quit, interviewees considered e-cigarettes to be safer than traditional cigarettes. A recent relevant survey found (Hefner et al., 2016) that, as in the general population, many individuals with mental conditions do believe that e-cigarettes are less harmful than traditional cigarettes.

In relation to the findings on e-cigarette use, a recent study by Miller et al. (2017) asked their participants with schizophrenia spectrum disorders about the advantages/disadvantages of e-cigarette use. In this study, 23% reported that e-cigarettes might taste better than traditional cigarettes and 10% that they might taste unpleasant; 27% reported that e-cigarettes might satisfy the desire to smoke and 13% that they might not satisfy their desire to smoke. In the same survey, when comparing the health effects of smoking and vaping, e-cigarettes were considered more harmful by 17% of participants, equally harmful by 17% of participants, less harmful by 34% of participants and 32% reported 'don't know' as their answer. Finally, relating to disadvantages of e-cigarette use, 17% reported that e-cigarettes might be inconvenient to use compared with smoking.

Overall, the qualitative study conducted as part of this thesis resulted in findings consistent with the other limited literature on this topic. It found that smokers with schizophrenia spectrum disorders perceived traditional cigarettes quite differently from e-cigarettes. In particular, they reported that for them, tobacco cigarettes were

easy to use, tasty, enjoyable and satisfying, with a perceived positive effect on their psychological health and useful to structure their time during the day. In contrast, e-cigarettes were perceived as not as easy to use, less enjoyable and satisfying compared with traditional cigarettes, but perceived as less harmful than smoking traditional cigarettes.

Question 2: *How appealing are licensed cessation aids for smoking cessation or reduction?*

Many participants had heard about only two types of NRT, specifically patches and gum, despite the evidence regarding efficacy of a wider range of licensed cessation aids for smokers with schizophrenia spectrum disorders (Cahil et al., 2014; Anthenelli et al., 2016). Most participants in both groups believed NRT was ineffective for helping them quit smoking or reduce cigarette consumption. Similar findings are reported in a recent qualitative study conducted by Meurk et al. (2016). Despite this perception, most participants were interested in using a nicotine patch, gum or mouth spray and reported their choice was influenced by either the cost of the product or what they had seen on TV.

All participants in both groups were not aware of varenicline or bupropion. The qualitative findings indicate the importance of improving activities to progress awareness of licensed medications to stop smoking in Italian smokers with schizophrenia spectrum disorders. Findings from this study (given the gaps in knowledge and awareness) also suggest that smokers with schizophrenia spectrum disorders should receive more smoking cessation advice. Other recent research has suggested that they do not receive information about smoking cessation aids (Mitchell et al., 2015) and a survey of US psychiatrists reported that they routinely deliver smoking cessation advice to only 12.5% of their patients (Himelhoch & Daumit, 2003).

Question 3, *How appealing are e-cigarettes for smoking cessation or reduction?*

The qualitative study findings suggested that smokers' views regarding the appeal of e-cigarettes were complex, but that they could be promising for modifying smoking behaviour. Finding from the qualitative study were that e-cigarettes

specifically for smoking cessation or reduction were appealing for about half of the participants in the whole sample (16 of 30) and principally in the majority (12) of participants who were from the group motivated to stop smoking. It emerged that smokers with schizophrenia spectrum disorders who reported that e-cigarettes might be appealing for cessation or reduction believed that they were safer for their own health compared with traditional cigarettes and were interested in switching. Thus, compared with licensed aids for smoking cessation and reduction, e-cigarettes may have greater appeal. This should be taken into account in order to assist people with schizophrenia to quit or reduce smoking.

This finding is supported by recent results from other studies that suggest that in individuals with serious mental illness, including schizophrenia spectrum disorders, e-cigarettes may appeal as a possible alternative to smoking (Hefner et al., 2016). Other studies have also found that mental health patients perceive e-cigarettes as a viable aid to smoking cessation and/or reducing traditional daily cigarettes consumption (Cummins et al., 2014; Hefner et al., 2017; Pratt et al., 2016).

6.3 E-cigarettes for smoking cessation and reduction in people with schizophrenia spectrum disorders

This section revisits the three research questions developed to inform the design and conduct of the single arm pilot study included in Chapter 4 and reflects on findings in the context of the wider literature. Each of the original research questions is discussed in turn.

Question 1: *Will the participants quit smoking if they use this e-cigarette?*

The single arm pilot study outlined in Chapter 4 demonstrated that the use of e-cigarettes in this study were feasible and acceptable for promoting smoking cessation amongst participants. In addition, vaping for smoking cessation appeared effective, at least in terms of very preliminary findings from this small study. Here smoking abstinence was defined as sustained self-reported abstinence from tobacco smoking for the 30-day period prior to the last three-month study visit. CO levels were measured to verify CO concentration of ≤ 10 ppm for the quitters according to the Russell standard (West et al., 2005). Sixteen participants (40%) completely switched to e-cigarettes and stopped smoking.

These promising findings on the possible effectiveness of vaping for smoking cessation in this population add to the existing, but very sparse, literature on this topic. Few and small studies offer relevant and recent data about the effectiveness of e-cigarettes for smoking cessation in smokers with schizophrenia spectrum disorders. For example, a recent study comparing nicotine patch and e-cigarettes in smokers with mental illnesses showed similar effectiveness of e-cigarettes and nicotine patch for smoking cessation in 24 smokers who reported use of antipsychotic drugs (O'Brien et al., 2015). Amongst this subgroup, differences between treatments were not statistically significant for cessation (patch 14% [5/35], 16 mg e-cigarette 5% [2/39], 0 mg e-cigarette 0% [0/12], $p = 0.245$), AEs or relapse rates. This was a secondary analysis of data from the ASCEND trial in New Zealand involving 657 dependent adult smokers motivated to quit, randomised to 16 mg nicotine e-cigarette, 21 mg nicotine patch, or 0 mg nicotine e-cigarette, where the authors identified 86 participants with mental illnesses by using self-reported medication use and the Anatomical Therapeutic Chemical Classification System, of which 28% (24/86) reported use of antipsychotics.

A second study found that in 21 smokers with serious mental illnesses who were offered an e-cigarette for four weeks, two participants self-reported abstinence from traditional cigarettes (Pratt et al., 2016). In a more recent study, Hickling et al. (2018) reported that at the 24-week follow up visit, only one of 50 participants enrolled in this study quit smoking. The current study adds to a promising literature, therefore, in studies with a high priority group for smoking cessation. E-cigarettes may be effective for smoking cessation in this target group, but the impact of e-cigarettes for smoking cessation needs to be explored by additional well-controlled studies with larger sample sizes.

Question 2: *Will the participants reduce the number of cigarettes smoked if they use this e-cigarette?*

In the single arm pilot study, e-cigarette use facilitated smoking reduction amongst patients who didn't want to quit smoking and was related to changes in their smoking behaviour such as 50% or greater reduction in their daily cigarette consumption. We observed a sustained 50% reduction, CO verified, in the number of traditional cigarettes smoked per day at week-12 amongst 52.5% (21/40) of participants.

Amongst 17 participants (excluding quitters), Pratt et al. (2016) reported a significant decrease in cigarettes per week between BL (204.5) and the end of the FOUR-week supply of e-cigarettes (75) and in the study conducted by Hickling et al. (2018) 10 participants (25%) achieved $\geq 50\%$ reduction in CPD.

Smoking is well documented to be associated with a host of illnesses, including hypertension, CVDs, cancer, and COPD. These results, associated with other data indicating that 86.2% of those with mental illness who used e-cigarettes were also using traditional cigarettes (Hefner et al., 2016), support the possibility that dual usage may be more prevalent in adults with mental illnesses than in the general population (Berg et al., 2015; Dawkins et al., 2013). However, it is also important to consider that a recent study of Shahab et al. (2017), discussed in more depth in Chapter 2 of this thesis, did not support dual use for harm reduction.

A recent Cochrane review found that in the general population, e-cigarettes may help smokers reduce the number of traditional CPD compared with placebo (McRobbie et al., 2014). Reducing the number of traditional cigarettes smoked may be a strategy (or pathway) towards future complete cessation and may lead to less exposure to dangerous toxicants than continued smoking of traditional cigarettes (Lindson-Hawley et al., 2012). However, this hypothesis remains to be tested.

In another study, smokers who used e-cigarettes as part of smoking cessation treatment, and who failed in their attempt to quit smoking but reduced their daily cigarette consumption and continued to use e-cigarettes, were exposed to fewer toxicants compared with those who continued to smoke only traditional cigarettes, suggesting that the smoking reduction was associated with harm reduction (McRobbie et al., 2015). In the current single arm pilot study, we could not quantify harm reduction from cutting down the number of CPD while using an e-cigarette, but this is a viable area for future research with patients with schizophrenia.

Question 3: *Are the study procedures feasible, and are they acceptable to participants?*

To answer this question, the focus of the current research was on the acceptability and feasibility of the intervention for smokers with schizophrenia spectrum

disorders. In terms of feasibility, the research found the study procedures were acceptable to the smokers because negative impacts on the physical and mental health of participants following e-cigarette use (based on the measures we were able to collect) were not observed. In addition, early signs of harm reduction in terms of BP, HR and CO reduction were promising.

In detail, fully described in the Chapter 4 of this thesis (Section 4.5.4), participants who completed the study showed improvements in BP and HR without weight gain. AEs typical of smoking withdrawal symptoms such as depression, anxiety, insomnia, irritability, hunger, and constipation were not reported. Also, there were no reported SAEs during the study. Another explanation for the relative acceptability may be attributed to the satisfaction related to the e-cigarette used in this study as assessed by mCEQ.

Psychopathological exacerbations (assessed by the SAPS and SANS scales) during the study procedures were not observed and positive and negative symptoms of schizophrenia maintained their stability during the study procedures. Participants also reported that using the e-cigarettes provided satisfaction. The e-cigarette (JUUL) was easy and simple to use. The device is breath actuated, has no user modifiable settings, has a fixed battery with battery regulation features, has a nicotine pharmacokinetic profile similar to traditional cigarettes, and its technology avoids the “dry puff” phenomenon (Jensen, 2015).

Previous research has suggested that adherence to an intervention is more likely if the products used are acceptable to participants. Considering that attrition rates in smoking cessation studies have been found to be particularly high (Belita & Sidani, 2015), the low attrition rate observed in the current study conducted as part of this PhD research could be considered as a further sign of the study’s acceptability.

6.4 Reflections on the qualitative and quantitative research and implications for the proposed future RCT

The extant literature on e-cigarette use amongst adults with schizophrenia spectrum disorders is limited, yet gradually growing. E-cigarettes have sparked a debate within the public health community as to their potential benefits as a tool for cessation and/or harm reduction (Wagener et al., 2012).

Each study (qualitative and quantitative) conducted as a part of this dissertation provided findings that can be used to inform public health professionals and researchers regarding perceptions of e-cigarette products held by smokers with schizophrenia. In addition, the findings provide insight into the complex relationship between e-cigarette use and traditional cigarette smoking. Again, both the qualitative study (Chapter 3) and quantitative study (Chapter 4) combined to inform the protocol for a future trial (Chapter 5).

In the qualitative study, amongst smokers not motivated to quit, the taste of traditional cigarettes was considered fundamental to their smoking experience. Tobacco flavor cartridges/pods were used in the single arm pilot study with a good level of acceptability and satisfaction and the same flavour was maintained for the RCT protocol. A third of the qualitative study sample were unaware of how much e-cigarettes cost, with the other two thirds relatively equally split as to whether they thought they were more or less expensive compared with traditional cigarettes. It is important to understand if smokers know the average cost of e-cigarettes (and how they perceive the cost) and know how much money they spend per week to smoke their traditional cigarettes; if smokers believe e-cigarettes are too expensive, this may be a barrier to future use or attractiveness/appeal. It is also important to consider that continuous use of the e-cigarette used in this study can in the long run be more expensive than e-cigarettes with liquid, but the JUUL model is certainly simpler and easier to use and does not waste time or require complicated operations to change components. We used an affordable product for the single arm pilot study, and its suggested effectiveness led us to include it in the RCT protocol. The starter kit costs about 45 euros and each pod/cartridge about three euros. Considering that our participants smoked about 30 cigarettes per day and that cigarettes in Italy cost about 5.50 euros, our participants would have spent about 460 euros in 12 weeks. In contrast, those who quit smoking traditional cigarettes used e-cigarettes to an economic value of about 295 euros, saving hypothetically 165 euro in 12 weeks. However, longitudinal research with longer term follow-up is needed to confirm this.

The first study qualitatively explored the relationship with the participants' own traditional cigarette smoking and findings from this study support the notion that for smokers with schizophrenia spectrum disorders, smoking their own traditional

cigarettes provided a perceived positive effect on their mental health status, for example by helping them feel less anxious, depressed, and stressed, and smoking their own traditional cigarettes was also perceived as an aid to structuring their time and occupying the day. For these reasons it was decided to include in the RCT study protocol brief counseling support at each study visit, to help these smokers manage and better deal with the aspects highlighted above.

In the quantitative study all participants who had stopped or reduced smoking traditional cigarettes continued to use e-cigarettes for three months. However, the short duration of the single arm pilot study did not allow investigation of further changes in traditional cigarette smoking in the case of extended use of e-cigarettes, for example for an additional three months. In addition, many participants asked to have e-cigarettes for a further three months and more counselling to quit smoking. As a result, the RCT protocol proposed a programme with e-cigarette pods/cartridges provided for a total of 24 weeks, with follow-up until one year (52 weeks). This would have the aim of measuring the long-term impact on the variation in quality of life, possible development of dependence on e-cigarettes, and possible harm reduction effects by variation in cardiovascular parameters (BP and HR) and weight gain. In addition, a brief smoking cessation counselling intervention would be added to help smokers first to switch to the e-cigarette and progressively to become totally smoke and vape free.

Other reflections are relevant to future research and were identified during the quantitative study. A problem that was encountered was the long duration of the data collection visits due to the administration of SAPS and SANS at each visit. As a result, in the RCT protocol the two scales would be carried out every three months. In the quantitative study we included smokers who smoked at least 20 cigarettes daily, excluding many potential smokers who smoke fewer than 20 cigarettes daily; for this reason, the RCT protocol includes people who smoke 10 or more CPD. Limitations exist in both the qualitative and quantitative studies, particularly regarding the representativeness of the sample, as in the current work this was limited to Italian smokers with schizophrenia spectrum disorders. Considering this aspect, the RCT protocol has been designed as a multisite international study.

Finally, in the single arm pilot study, participants expressed positive attitudes towards e-cigarettes. During this study, many smokers with and without mental health illness were intrigued by this new form of e-cigarette. The researcher observed satisfaction in those who used it and that participants stopped smoking or significantly reduced the number of traditional cigarettes smoked per day. Also several people who referred our participants to these studies, including relatives, caregivers, psychiatrist, nurses and psychologists, asked where they could buy the product and use it to quit or reduce their traditional cigarette smoking. Considering all these elements, it would be worth considering whether the proposed RCT protocol as outlined in Chapter 6 would benefit from the addition of an embedded qualitative process evaluation.

With this in mind, future work could examine differences in attitudes and beliefs about e-cigarettes by users of different types of devices, for example. This could include participants who use products that closely resemble cigarette products (“cigalikes”) versus those who use more customizable devices (“tank systems” or “mods”) or even the new RRP (Reduced risks products): heat-not-burn products. These device types can differ in significant ways that affect users’ experience (e.g., availability of flavors; effective delivery of nicotine) which, in turn, might affect behaviour, acceptability, appeal, attitudes, and beliefs about the products. The existence of multiple user groups may have implications for the public health impact of e-cigarette use, RRP use and marketing.

A further area for consideration in future RCTs is economic analysis. It is well known that the costs of smoking fall on many different parts of society, especially on individuals with schizophrenia and their families and caregivers (Andrew et al., 2012). In terms of economic evaluation, few analyses have specifically addressed the question of the economic benefits and consequences of treatments intended to help people with schizophrenia spectrum disorders to quit or reduce smoking. In the framework of healthcare, an economic evaluation is just the comparison of two clinical interventions, for example usual care current practice versus a proposed replacement/alternative, in terms of costs and consequences (Drummond et al., 1997). The method in which consequences are measured would determine whether an economic evaluation is a cost effectiveness analysis (CEA: outcome generally measured in natural units such as number of hospital days avoided or life years

gained), a cost-utility analysis (CUA: outcome measured in terms of health-related utility), or a cost-benefit analysis (CBA: outcome measured in monetary terms). Schizophrenia spectrum disorders and tobacco addictions have very significant economic consequences.

A recent and instructive analysis used a Markov model to provide an economic evaluation of two months' treatment of bupropion and co-interventions (group therapy either alone or in combination with NRT) and compared this to co-interventions only. The model estimated that the incremental cost-effectiveness ratio of the combined intervention was £385 per QALY, well below NICE's recommended threshold for cost effectiveness. The model predicted that there was a 95% chance that the combined intervention was more cost-effective than the co-interventions alone (Winterbourne, 2012). Furthermore, a recent study Barnett et al. (2015) estimated that smokers the psychiatric illnesses who quit smoking at 41 years of age will realize a discounted gain of 0.83 QALYs or 1.14 life-years. This advantage is lower than the typical value of two QALYs per quit benefit calculated for smokers without mental health illnesses (Song et al., 2002; Godfrey et al., 2005), reflecting the higher non-smoking mortality hazard and lower health-related quality of life associated with serious mental diseases. Although these authors estimated the benefit per quit to be to be lower in smokers with mental health disorders than in smokers generally, this study showed that the intervention was still highly cost-effective.

Thus overall, an expanded protocol for a future RCT could consider an embedded additional process evaluation and could include an economic evaluation. An amended RCT protocol could emerge following the PhD.

6.4.1 Emerging implications

This PhD research has implications for future research and public health interventions, as well as for informing the debate surrounding e-cigarette products. Additionally, this dissertation research highlights the value of mixed methods approaches given that, looked at in isolation, the findings from the quantitative or qualitative studies could lead to very different conclusions. For example, based on the qualitative findings amongst not motivated-to-quit smokers, we might not expect

the high success rates that were observed in the quantitative results as a result of e-cigarette use.

Lastly, smokers with schizophrenia spectrum disorders in the qualitative study reported a lack of information about varenicline and bupropion as licensed smoking cessation aids. Beyond the proposed future research on e-cigarettes for smoking cessation amongst patients with schizophrenia, there would be merit in future research on these licensed medications with this group.

6.5 Strengths and limitations

Considering the chapters presented within this thesis as a collective body of work, some strengths and limitations should be recognized when evaluating the results and the implications of the findings.

6.5.1 Strengths

A multidimensional approach was used throughout this thesis: reviews of literature in multiple disciplines followed by a mixed-methods approach with three empirical studies, one qualitative study, one quantitative single arm pilot study, a structured protocol for a large RCT.

The study has an international and multi-disciplinary collaboration because it involved experts from five European and US universities with training deriving from psychology, medicine, public health and nursing.

The methodology used to develop the protocol for the large RCT has been reported in a transparent manner. The benefit of this is the mixture of the individual strengths of these methods. Many chapters reached similar conclusions despite the different methods used in each chapter. Each chapter provides new information to the body of research about e-cigarettes for smokers with schizophrenia spectrum disorders. Perception, appeal, acceptability and feasibility of e-cigarettes for smoking cessation or reduction for smokers with schizophrenia spectrum disorders have been tested in the qualitative and quantitative research phases of the development of this e-cigarette intervention.

The interactive essence of the development process means that findings from Chapters 3 and 4 can be applied to modify and improve the study protocol and the content of the intervention for a future large RCT.

This is the first qualitative study evaluating the perception of licensed smoking cessation therapies and e-cigarettes in smokers with schizophrenia spectrum disorders motivated and not motivated to quit.

Finally, this is the first behavioural study using JUUL and, with the exception of the Hickling et al. study (2018), the largest smoking cessation/reduction study of e-cigarettes in people with schizophrenia spectrum disorders.

6.5.2 Limitations

A number of limitations arise from the research in this thesis. First, the presentation of findings and results in the two studies (qualitative and quantitative) should only be taken as descriptions of selected representative samples of smokers with schizophrenia spectrum disorders from a specific geographic area of Sicily in Italy. This means the results may not be applicable to comparable populations elsewhere.

Secondly, using JUUL can also be a limitation for several reasons: it's unlike other e-cigarette models so the findings may not generalise to other devices; it's available only in the US, Canada, Israel, Switzerland, Russia, UK and Germany at the time of writing, and ongoing costs seem likely to be higher than for refillable e-cigarettes.

Third, a very important limitation is that this thesis represents a preliminary stage in introducing a complex intervention (replacing one socially constructed behaviour, and product, with another) with patients with schizophrenia.

A further limitation is that the included research cannot comment on the efficacy of an e-cigarette intervention for smoking cessation and reduction for smokers with schizophrenia spectrum disorders. The results were preliminary and involved qualitative research and a single arm pilot study. Hence, issues relating to the sample recruited for the qualitative study and for the single arm pilot quantitative study need to be addressed. In particular, a small sample means that findings would

not be generalizable to a larger population. This limitation has been highlighted in Chapter 4 and the larger trial proposed in Chapter 5, could help address this.

6.6 Reflection on my role in the research

As a PhD student preparing this thesis, I designed and carried out the studies. Thus, at this stage, I think it is important to outline my personal background and the perspective from which I managed this thesis.

Prior to beginning this PhD, I worked in research and clinical practice regarding schizophrenia, smoking addiction, e-cigarettes and harm reduction. Specifically, It is important to note that while completing the PhD (which was part-time for the first two years) I worked as clinical psychologist/psychotherapist and researcher at the smoking cessation research center of the University of Catania and at the department of mental health with patients with schizophrenia from 2004.

As consequence, I had access to support from other staff and a good site for recruitment.

My qualifications are in clinical psychology and psychotherapy. Reflecting on the advantages that background brought to the thesis, it meant that I already had some relevant expertise in the topic.

My approach to the thesis was undoubtedly shaped by my prior experience, either in research or with the target population. However, some aspects of the research were new to me. For example, I had not been involved in qualitative studies before. I therefore found the interviewing process a bit challenging. I experienced barriers in speaking to participants as they exhibited typical signs of schizophrenia syndrome which can make conversation (interviews) difficult.

Support from my supervisors assisted in developing my interviewing skills and also in interpreting the findings of my interviews. In contrast, however, the fact that I was familiar with the target group and the smoking cessation center setting facilitated recruitment.

6.7 Implications for the intervention by a large multisite randomised controlled trial with long-term follow-up and for clinical practice

Generally, results of the single arm pilot study show potential for investigating the effects of the intervention in a larger sample and in a real-life setting. The smoking cessation/reduction intervention looks to be acceptable to smokers with schizophrenia spectrum disorders and is feasible in practice. Further multisite RCT research with long-term follow up is needed to test if the intervention has the intended positive effect on smokers with schizophrenia spectrum disorders and could inform health authorities about the possibility of considering e-cigarettes as licensed smoking cessation/reduction aids.

According to the guidelines of the Italian Ministry of Health to quit smoking (OSSFAD, 2008), smokers with schizophrenia should be advised to stop smoking using licensed aids such as NRT, varenicline or bupropion in combination with behavioural individual or group support. However, this does not always happen in practice. Beyond official guidelines, other researchers (i.e. Sharma et al., 2017b) have suggested that smokers with schizophrenia spectrum disorders who are not motivated to quit smoking traditional cigarettes by using licensed aids or who communicate interest in using e-cigarettes should be provided with full information.

This should include smoking cessation counselling that includes information about the pros and cons of switching to e-cigarettes, and support in their attempts to do so. However again, in Italy, this rarely happens in practice at the current time.

6.8 Implications for future research

The limited studies to date, including those in this PhD thesis, suggest that e-cigarettes can help smokers with schizophrenia spectrum disorders to quit or significantly reduce their smoking consumption without serious adverse effects, even in those not ready to quit (Caponnetto et al., 2013d; Sharma et al., 2017a; Pratt et al., 2016).

Considering the increased exposure to traditional cigarette use, high nicotine dependence, and difficulty quitting amongst this target group, greater attention and effort is warranted in future studies that assess the following: 1) harm reduction by

switching from traditional cigarettes to e-cigarettes or other RRP, 2) the role of nicotine level/preferences in initiation and maintenance of e-cigarette use, 3) the role of flavour preferences in initiation and maintenance of e-cigarette use, 4) the longitudinal physical and psychological impact of e-cigarette single use or dual use, 5) the variability in e-cigarette use and appeal across different diagnostic groups (e.g affective disorders, personality disorders, anxiety and obsessive disorders, substance abuse disorders, ADHD), 6) the impact of switching from traditional cigarettes to e-cigarettes in neurocognitive performance, 7) the impact of switching from traditional cigarettes to e-cigarettes on quality of life, 8) assessment of possible e-cigarette dependence development, 9) the impact of switching from traditional cigarettes to e-cigarettes on pharmacological and psychosocial treatments, 10) combining smoking cessation counselling and e-cigarettes and 11) strategies to improve smoking cessation activities delivered by health professionals involved in schizophrenia spectrum disorders rehabilitation.

Future interventions can draw on the body of information in this thesis. Arguably, the evidence is not only relevant for interventions to promote smoking cessation and smoking reduction for smokers with schizophrenia spectrum disorders, but potentially relevant for a wide range of smoking populations.

Principally, the use of new generation e-cigarettes combined with smoking cessation counselling could be applied to promote health empowerment in inveterate smokers not motivated to quit or who have failed to quit with other smoking cessation treatments.

Evidence gathered in Chapter 3 regarding smokers' perceptions of traditional cigarettes, e-cigarettes and licensed smoking cessation/reduction aids, and evidence gathered in Chapter 4 regarding the feasibility and acceptability of an e-cigarette intervention for smokers with schizophrenia spectrum disorders not motivated to quit, may be relevant for future e-cigarette interventions delivered with smokers motivated to quit with or without schizophrenia.

6.9 Conclusion

In this thesis, I have: reviewed the scientific literature; consulted smokers with schizophrenia spectrum disorders in order to develop an effective, safe and acceptable intervention; and tested this intervention in a preliminary study leading to plans for future research.

This preliminary research indicates that the smoking cessation/reduction intervention using a new generation e-cigarette for smokers with schizophrenia spectrum disorders is: feasible; acceptable; and supports the body of theory and evidence described in this thesis. The work also highlights the need for a robust, well-controlled, large, multisite RCT with long-term follow-up.

Effective approaches are urgently needed to address the persistently high smoking rates in smokers with schizophrenia spectrum disorders. THR and potential health empowerment by switching to e-cigarettes could help to further reduce the health, financial and psychosocial parity gap experienced by this population.

Finally, it is worth emphasising the strengths of the intervention itself. E-cigarettes are a promising technology that replaces smoking with a less harmful alternative (based on the research to date) that still provides nicotine but with fewer or far lower levels of toxicants. Given the low success rates for smoking cessation in people with schizophrenia, alternatives are urgently needed. In addition, combining e-cigarettes with smoking cessation counselling that motivates people to change and sustain healthy behaviours has great potential.

The potential promise of this approach can be summarised by an unexpected finding outlined at the end of Chapter 5. This was that several individuals connected to our single arm pilot study participants (including relatives, caregivers, psychiatrists, nurses and psychologists) asked where they could buy the e-cigarette to use themselves to stop or reduce cigarette smoking. This suggests that during the process of researching an intervention to try to improve the health of a priority group for smoking cessation, wider benefits may have been achieved, even including prompting quit attempts in other associated populations.

REFERENCES

- Addington, J., el-Guebaly, N., Addington, D., & Hodgins, D. (1997). Readiness to stop smoking in schizophrenia. *The Canadian Journal of Psychiatry/La Revue canadienne de psychiatrie* 42(1), 49-52.
- Addington, J., el-Guebaly, N., Campbell, W., Hodgins, D. C., & Addington, D. (1998). Smoking cessation treatment for patients with schizophrenia. *The American Journal of Psychiatry*, 155(7), 974-6.
- Adriaens, K., Van Gucht, D., Declerck, P., & Baeyens, F. (2014). Effectiveness of the electronic cigarette: An eight-week Flemish study with six-month follow-up on smoking reduction, craving and experienced benefits and complaints. *International journal of environmental research and public health*, 11(11), 11220–11248.
- Aguilar, M. C., Gurpegui, M., Diaz, F. J., & de Leon, J. (2005). Nicotine dependence and symptoms in schizophrenia: naturalistic study of complex interactions. *Br J Psychiatry*, 186, 215–221.
- Alberg, A. J., & Samet, J. M., (2003). Epidemiology of lung cancer. *Chest*, 123, 21-49.
- Albuquerque, E. X., Pereira, E. F., Alkondon, M., and Rogers, S. W. (2009). Mammalian nicotinic acetylcholine receptors: from structure to function. *Physiol. Rev.* 89, 73–120.
- American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC: Author.
- Andreasen, N.C. (1983). The Scale for the Assessment of Negative Symptoms (SANS). Iowa City, Iowa: The University of Iowa.
- Andreasen, N.C. (1984). The Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, Iowa: The University of Iowa.
- Andresen, N.C., Flaum, M., Arndt, S., Alliger, R., & Swayze, V. W. (1991). Positive and negative symptoms: Assessment and validity. *Negative vs Positive Schizophrenia*. (pp. 28–51). Springer, Berlin, Heidelberg.
- Andrew, A., Knapp, M., McCrone, P., Parsonage, M., & Trachtenber, M. (2012). Effective Interventions in schizophrenia: the economic case.
- Anthenelli, R. M., Benowitz, N. L., West, R., St Aubin, L., McRae, T., Lawrence, D., et al. (2016). Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *The Lancet*, 387(10037), 2507-2520.

- Aubin, H. J., Rollema, H., Svensson, T. H., & Winterer, G. (2012). Smoking, quitting, and psychiatric disease: a review. *Neuroscience and Biobehavioral Reviews*, 36(1), 271–284.
- Backhaus, I., D'Egidio, V., Grassucci, D., Gelardini, M., Ardizzone, C., & La Torre, G. (2017). Link between perceived smoking behaviour at school and students smoking status: a large survey among Italian adolescents. *Public Health*, 151, 169-176.
- Baker, T.B., Brandon, T.H., Chassin, L (2004). Motivational Influences on Cigarette Smoking *Annual Review of Psychology*, 55(1), 463-491.
- Baker, A., Richmond, R., Haile, M., Lewin, T. J., Carr, V. J., Taylor, R. L., et al. (2006). A randomized controlled trial of a smoking cessation intervention among people with a psychotic disorder. *The American Journal of Psychiatry*, 163 (11), 1934-42.
- Baker, A., Richmond, R., Haile, M., Lewin, T. J., Carr, V. J., Taylor, R. L., et al. (2007). Characteristics of smokers with a psychotic disorder and implications for smoking interventions. *Psychiatry Research*, 150(2), 141–152.
- Ball & Tasaki (1992). The Role and Measurement of Attachment in Consumer Behavior. *Journal of Consumer Psychology*, 1, 155-172.
- Bandura, A., & Walters, R. H. (1963). *Social learning and personality development*. New York: Holt Rinehart and Winston.
- Barnett, P. G., Wong, W., Jeffers, A., Hall, & S. M., Prochaska, J. J. (2015). Cost effectiveness of smoking cessation treatment initiated during psychiatric hospitalization: Analysis from a randomized, controlled trial. *The Journal of clinical psychiatry*, 76(10), 1285–91.
- Barr, R. S., Culhane, M. A., Jubelt, L. E., Mufti, R. S., Dyer, M. A., Weiss, A. P., et al. (2008a). The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. *Neuropsychopharmacology*, 33(3), 480-90.
- Barr, A. M., Procyshyn, R. M., Hui, P., Johnson, J. L., & Honer, W. G. (2008b). Self-reported motivation to smoke in schizophrenia is related to antipsychotic drug treatment. *Schizophrenia Research*, 100(1-3), 252–260.
- Batki, S. L., Meszaros, Z. S., Strutynski, K., Dimmock, J. A., Leontieva, L., Ploutz-Snyder, R., et al. (2009). Medical comorbidity in patients with schizophrenia and alcohol dependence. *Schizophrenia research*, 107(2-3), 139–146.

- Bauld, L., Bell, K., McCullough, L., Richardson, L., & Greaves, L. (2010). The effectiveness of NHS smoking cessation services: a systematic review. *Journal of Public Health, 32* (1), 71-82.
- Beary, M., Hodgson, & R., Wildgust, H. J. (2012). A critical review of major mortality risk factors for all-cause mortality in first-episode schizophrenia: clinical and research implications. *Journal of Psychopharmacology, 26* (5suppl), 52–61.
- Belita, M., & Sidani, S. (2015). Attrition in Smoking Cessation Intervention Studies: A Systematic Review. *Canadian Journal of Nursing Research, 47*(4), 21–40.
- Bennett, M. E., Wilson, A. L., Genderson, M., & Saperstein, A. M. (2013). Smoking cessation in people with schizophrenia. *Current Drug Abuse Reviews, 6*(3), 180-90.
- Berg, C. J. (2015). Preferred flavors and reasons for e-cigarette use and discontinued use among never, current, and former smokers. *International journal of Public Health, 61*(2), 225–236.
- Berry, J. C. (1967). Antecedents of schizophrenia, impulsive character and alcoholism in males. *Paper presented at the 75th Annual Convention of the American Psychological Association*. Washington, DC.
- Biener, L., & Abrams, D. B. (1991). The Contemplation Ladder: Validation of a measure of cessation. *Health Psychology, 10*(5), 360-365.
- Boardman, T., Catley, D., Mayo, M. S., & Ahluwalia, J. S. (2005). Self-efficacy and motivation to quit during participation in a smoking cessation program. *International Journal of Behavioral Medicine, 12*(4), 266-272.
- Bolliger, C. T., Zellweger, J. P., Danielsson, T., van Biljon, X., Robidou, A., Westin, A., et al. (2000). Smoking reduction with oral nicotine inhalers: double blind, randomised clinical trial of efficacy and safety. *BMJ, 321*(7257), 329-333.
- Bourque, J., Lakis, J., Champagne, J., Stip E., Lalonde, P., Lipp, O., et al. (2013) Clozapine and visuospatial processing in treatment-resistant schizophrenia. *Cognitive Neuropsychiatry, 18*(6), 615-630.
- Boyatzis, R.E. (1998): Transforming qualitative information: thematic analysis and code development. Sage
- Bowen, D., Kreuter, M., Spring, B., Cofta-Woerpel, L., Linnan, L., Weiner, D., et al. (2009). How We Design Feasibility Studies. *American journal of preventive medicine, 36*(5), 452-457.
- Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative Research in Psychology, 3*(2), 77–101.

- Brose, L. S., Brown, J., Hitchman, S. C., & McNeill, A. (2015). Perceived relative harm of electronic cigarettes over time and impact on subsequent use. A survey with 1-year and 2-year follow-ups. *Drug and Alcohol dependence*, 157, 106-111.
- Brown, S., Inskip, H., & Barraclough, B. (2000). Causes of the excess mortality of schizophrenia. *The British journal of psychiatry*, 177(3), 212–217.
- Brown, C. H., Medoff, D., Dickerson, F. B., Fang, L. J., Lucksted, A., Goldberg, R. W., Dixon, L. B. (2015). Factors influencing implementation of smoking cessation treatment within community mental health centers. *Journal of dual diagnosis*, 11(2), 145–150.
- Brown, A. & Xing C. (2015) *Patent U.S. Patent 9*, 215-895.
- Bryman, A. (2012). *Social research methods*. Oxford university press.
- Briskman, I., Bar, G., Boaz, M., & Shargorodsky, M. (2012). Impact of Co-Morbid Mental Illness on the Diagnosis and Management of Patients Hospitalized for Medical Conditions in a General Hospital. *The International Journal of Psychiatry in Medicine*, 43(4), 339–348.
- Bullen, C., Howe, C., Laugesen, M., McRobbie, H., Parag, V., Willima, J., et al. (2013). Electronic cigarettes for smoking cessation: a randomized controlled trial. *The Lancet*, 382(9905), 1629–1637.
- Burns, D. M. (1991). Cigarettes and cigarette smoking. *Clinic in chest medicine*, 12(4), 631–642.
- Cahill, K., Stevens, S., Perera, R., & Lancaster, T. (2013). Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *The Cochrane database of systematic reviews*, 31(5).
- Cahill, K., Stevens, S., Lancaster, T. (2014). Pharmacological Treatments for Smoking Cessation. *JAMA*, 311(2), 193–194.
- Cahill, K., Lindson-Hawley, N., & Thomas, K. H. (2016). Nicotine receptor partial agonists for smoking cessation. *The Cochrane database of systematic reviews*, 18(4).
- Callaghan, R. C., Veldhuizen, S., Jeysingh, T., Orlan, C., Graham, C., Kakouris, G., et al. (2014). Patterns of tobacco-related mortality among individuals diagnosed with schizophrenia, bipolar disorder, or depression. *Journal of Psychiatric Research*, 48(1), 102-10.
- Campion, J., Shiers, D., Britton, J., Gilbody, S., Bradshaw, T (2014). Primary Care Guidance on Smoking and Mental Disorders – 2014 update; *Royal College of General Practitioners & Royal College of Psychiatrists*.

- Campagna, D., Cibella, F., Caponnetto, P., Amaradio, M. D., Caruso, M., Morjaria, J. B., et al. (2016). Changes in breathomics from a 1-year randomized smoking cessation trial of electronic cigarettes. *European Journal of Clinical Investigation*, *46*(8), 698-706.
- Caponnetto, P., Keller, E., Bruno, C. M., & Polosa, R. (2013a). Handling relapse in smoking cessation: strategies and recommendations. *Internal and Emergency Medicine*, *8*(1), 7–12.
- Caponnetto, P., Russo, C., Bruno, C. M., Alamo, A., Amaradio, M. D., & Polosa, R. (2013b). Electronic cigarette: a possible substitute for cigarette dependence. *Monaldi Archives for Chest Disease: archivio Monaldi per le malattie del torace*, *79*(1), 12–19.
- Caponnetto, P., Campagna, D., Cibella, F., Morjaria, J. B., Caruso, M., Russo, C., et al. (2013c). Correction: Efficiency and Safety of an eElectronicigarette (ECLAT) as Tobacco Cigarettes Substitute: A Prospective 12-Month Randomized Control Design Study. *PLoS ONE* *9*(1).
- Caponnetto, P., Auditore, R., Russo, C., Cappello G. C., & Polosa, R. (2013d). Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study. *International Journal of Environmental Research and Public Health*, *10*(2), 446-61.
- Caponnetto P (2014). Silver linings and improvement of our resources for smoking cessation interventions. e-Letter, Tobacco Control BMJ12 jun 2014<https://tobaccocontrol.bmj.com/content/silver-linings-and-improvement-our-resources-smoking-cessation-interventions>
- Caponnetto, P., Polosa, R., Auditore, R., Minutolo, G., Signorelli, M., Maglia, M., et al. (2014). Smoking Cessation and Reduction in Schizophrenia (SCARIS) with e-cigarette: study protocol for a randomized control trial. *Trials*, *15*(1), 88.
- Cappelleri, J. C., Bushmakin, A. G., Baker, C. L., Merikle, E., Olufade, A. O., & Gilbert, D. G. (2007). Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. *Addictive Behaviors*, *32*(5), 912-923.
- Carney, C. P., Jones, L., & Woolson, R. F. (2006). Medical comorbidity in women and men with schizophrenia: a population-based controlled study. *Journal of general internal medicine*, *21*(11), 1133–1137.
- Carpenter, C.M., Wayne, G.F., Connolly, G.N. (2007). The role of sensory perception in the development and targeting of tobacco products. *Addiction*, *102*, 136–147.
- Carpenter, M. J., Heckman, B. W., Wahlquist, A. E., Wagener, T. L., Goniewicz, M. L., Gray, K. M., et al. (2017). A naturalistic, randomized pilot trial of E-cigarettes:

uptake, exposure, and behavioral effects. *Cancer Epidemiology and Prevention Biomarkers*, 26(12), 1-9.

- Cather, C., Dyer, M. A., Burrell, H. A., Hoepfner B., Goff, D. C., & Evins, A. E. (2013). An open trial of relapse prevention therapy for smokers with schizophrenia. *Journal of Dual Diagnosis*, 9(1), 87-93.
- Cather, C., Pachas, G.N., Cieslak, K.M., Evins, A.E. (2017). Achieving Smoking Cessation in Individuals with Schizophrenia: Special Considerations. *CNS Drugs*, 31, 471.
- Celermajer, D. S., Sorensen, K. E., Gooch, V. M., Spiegelhalter, D. J., Miller, O. I., Sullivan, I. D., et al. (1992). Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet*, 340(8828), 1111–1115.
- Charmaz, K. (2006). *Constructing Grounded Theory A Practical Guide Through Qualitative Analysis*. New Delhi: Sage.
- Chen, L. S., Baker, T., Brownson, R. C., Carney, R. M., Jorenby, D., Hartz, S., et al. (2016). Smoking Cessation and Electronic Cigarettes in Community Mental Health Centers: Patient and Provider Perspectives. *Community Ment Health*, 53(6), 695-702.
- Chen, R., Aherrera, C., Isicheye, P., Olmedo, S., Jarmul, J., Cohen, A., et al. (2017). Assessment of indoor air quality at an electronic cigarette (vaping) convention. *Journal of Exposure Science and Environmental Epidemiology*, 1.
- Chou, K. R., Chen, R., Lee, J. F., Ku, C. H., & Lu, R. B. (2004). The effectiveness of nicotine-patch therapy for smoking cessation in patients with schizophrenia. *International Journal of Nursing Studies*, 41(3), 321-30.
- Chue, P., & Lalonde, J.K., (2014). Addressing the unmet needs of patients with persistent negative symptoms of schizophrenia: emerging pharmacological treatment options. *Neuropsychiatric disease and treatment*, 10, 777–789.
- Cibella, F., Campagna, D., Caponnetto, P., Amaradio, M. D., Caruso, M., Russo, C., et al. (2016). Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. *Clinical Science*, 130(21), 1929-1937.
- Cobb, N. K., Byron, M. J., Abrams, D. B., & Shields, P. G. (2010). Novel nicotine delivery systems and public health: The rise of the "e-cigarette". *American Journal of Public Health*, 100, 2340-2342.
- Cohen, L., Manion, L., & Morrison, K. (2011). *Research methods in education* (7th ed.). New York, NY: Routledge.

- Conners, C. K. & Staff M. H. S. (2000). *Conners' Continuous Performance Test II: Computer Program for Windows Technical Guide and Software Manual*. North Tonawanda, NY: Multi-Health Systems.
- Conrad, A. (2011). Exposure to tobacco smoke. *Cigarette Smoke Toxicity: Linking Individual Chemicals to Human Diseases*, 67-91.
- Cook, B. L., Wayne, G. F., Kafali, E. N., Liu, Z., Shu, C., & Flores, M. (2014). Trends in smoking among adults with mental illness and association between mental health treatment and smoking cessation. *JAMA*, 311(2), 172-82.
- Cooke, W. H., Pokhrel A., Dowling, C., Fogt, D. L., & Rickards, C. A. (2015). Acute inhalation of vaporized nicotine increases arterial pressure in young non-smokers: A pilot study. *Clinical Autonomic Research*, 25(4), 267-270.
- Cravo, A. S., Bush, J., Sharma, G., Savioz, R., Martin, C., Craige, S., et al. (2016). A randomised, parallel group study to evaluate the safety profile of an electronic vapour product over 12 weeks. *Regulatory Toxicology and Pharmacology*, 81, S1-S14.
- Creswell, J. W. (1998). *Qualitative inquiry and research design: Choosing among five traditions*. Thousand Oaks, CA, US: Sage Publications, Inc.
- Cummins, S. E., Zhu, S. H., Tedeschi, G. J., Gamst, A. C., & Myers, M. G., (2014). Use of e-cigarettes by individuals with mental health conditions. *Tobacco Control*, 23(3), 48–53.
- Dalack, G. W., Becks, L., Hill, E., Pomerleau, O. F., & Meador-Woodruff, J. H. (1999). Nicotine withdrawal and psychiatric symptoms in cigarette smokers with schizophrenia. *Neuropsychopharmacology* 21(2), 195–202.
- Dalack, G. W., & Meador-Woodruff, J. H. (1999). Acute feasibility and safety of a smoking reduction strategy for smokers with schizophrenia. *Nicotine & tobacco research*, 1(1), 53–57.
- Davis, S. C. (2014). Annual Report of the Chief Medical Officer 2013: Public Mental Health Priorities-Investing in the Evidence. *Department of Health*.
- Dawkins, L., Turner, J., Roberts, A., & Soar, K., (2013). 'Vaping' profiles and preferences: An online survey of electronic cigarette users. *Addiction*, 108(6), 1115–1125.
- Dawkins, L., & Corcoran, O. (2014). Acute electronic cigarette use: Nicotine delivery and subjective effects in regular users. *Psychopharmacology*, 231(2), 401–407.

- Dawkins, L., Munafo, M., Christoforou, G., Olumegbon, N., & Soar, K. (2016). The effects of e-cigarette visual appearance on craving and withdrawal symptoms in abstinent smokers. *Psychology of addictive behaviors, 30*(1), 101–105.
- de Leon, J., Diaz, F. J., Rogers, T., Browne, D., Dinsmore, L., (2002). Initiation of daily smoking and nicotine dependence in schizophrenia and mood disorders. *Schizophr. Res. 56*, 47-54.
- de Leon, J., & Diaz, F. J. (2005). A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophrenia research, 76*(2-3), 135–157.
- De Marco, R., Accordini, S., Cerveri, I., Corsico, A., Sunyer, J., Neukirch, F., et al. (2004). An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. *Thorax, 59*(2), 120-125.
- De Meo, D. L., Carey, V. J., Chapman, H. A., Reilly, J. J., Ginns, L. C., Speizer, F. E., et al. (2004). Familial aggregation of FEF25–75 and FEF25–75/FVC in families with severe, early onset COPD. *Thorax, 59*(5), 396-400.
- De Santis, L., Noel Ugarriza, D. (2000). The concept of theme as used in qualitative nursing research. *West. J. Nurs. Res. 22*, 351–372.
- Devlin, N., & Brooks, R. (2017). EQ-5D and the EuroQol group: Past, present, future. *Applied Health Economics and Health Policy, 15*(2), 127–137.
- Diaz, F. J., James, D., Botts, S., Maw, L., Susce, M. T., & De Leon, J. (2009). Tobacco smoking behaviors in bipolar disorder: a comparison of the general population, schizophrenia, and major depression. *Bipolar Disorders, 11*(2), 154–165.
- Dickerson, F., Stallings, C., Origoni, A. E., Vaughan, C., Khushalani, S., Schroeder, J., et al. (2013). Cigarette smoking among persons with schizophrenia or bipolar disorder in routine clinical settings, 1999–2011. *Psychiatric services, 64*(1), 44–50.
- DiFranza, J. R., & Lew, R. A. (1996). Morbidity and mortality in children associated with use of tobacco products by other people. *Pediatrics, 97*(4), 560-568.
- Dixon, L., Medoff, D. R., Wohlheiter, K., Goldberg, C., Kreyenbuhl, R., Adams, J., et al. (2007). Correlates of severity of smoking among persons with severe mental illness. *American Journal on Addiction, 16*(2), 101–110.
- Doll, R., Peto, R., Boreham, J., & Sutherland, I. (2004). Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ, 328*(7455), 1519–1528.

- D'ruiz, C. D., O'connell, G., Graff, D. W., & Yan, X. S. (2017). Measurement of cardiovascular and pulmonary function endpoints and other physiological effects following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers. *Regulatory Toxicology and Pharmacology*, *87*, 36-53.
- Drummond, M. F., O'Brien, B., Stoddart, G. L., & Torrance, G. W. (1997). *Methods for the Economic Evaluation of Health Care Programmes*. Oxford: Oxford University Press.
- D'Souza, M. S., & Markou, A. (2012). Schizophrenia and tobacco smoking comorbidity: nAChR agonists in the treatment of schizophrenia-associated cognitive deficits. *Neuropharmacology*, *62*(3), 1564-1573.
- D'Souza, D. C., Esterlis, I., Carbuto, M., Krasenics, M., Seibyl, J., Bois, F., et al. (2012). Lower $\beta 2^*$ -nicotinic acetylcholine receptor availability in smokers with schizophrenia. *The American Journal of Psychiatry*, *169*(3), 326-34.
- Duffy, S. A., Kilbourne, A. M., Austin, K. L., Dalack, G. W., Woltmann, E. M., Waxmonsky, J., & Noonan, D. (2012). Risk of smoking and receipt of cessation services among veterans with mental disorders. *Psychiatric services (Washington, D.C.)*, *63*(4), 325–332.
- El Dib, R., Suzumura, E. A., Akl, H., Gomaa, A., Agarwal, Y., Chang, M., et al. (2017). Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: A systematic review and meta-analysis. *BMJ open*, *7*(2), e012680.
- Elis, O., Caponigro, J. M., & Kring, A. M. (2013). Psychosocial treatments for negative symptoms in schizophrenia: Current practices and future directions. *Clinical Psychology Review*, *33*(8), 914-928.
- Eldridge, S. M., Lancaster, G. A., Campbell, M. J., Thabane, L., Hopewell, S., Coleman, C. L., et al. (2016). Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework. *PLoS ONE*, *11*(3).
- Ellenbroek B. A. (2012). Psychopharmacological treatment of schizophrenia: what do we have, and what could we get? *Neuropharmacology* *62*, 1371-1380.
- Esterberg, M., & Compton, M. (2005). Smoking behavior in persons with schizophreniaspectrum disorder: A qualitative investigation of the transtheoretical model. *Social Science and Medicine*, *61*, 293–303.
- Esterlis, I., Bois, F., Pittman, B., Picciotto, M. R., Shearer, L., Anticevic, A., et al. (2013). In vivo evidence for B2 nicotinic acetylcholine receptor subunit upregulation in smokers as compared with nonsmokers with schizophrenia. *Biological Psychiatry*, *76*(6), 495-502.

- Etter, J. F. (2010). Electronic cigarettes: a survey of users. *BMC public health*, 10(1), 231.
- Etter, J.F, Bullen, C. (2011). Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction*, 106, 2017–2028.
- Etter, M., Mohr, S., Garin, C., & Etter, J. F. (2004). Stages of change in smokers with schizophrenia or schizoaffective disorder and in the general population. *Schizophrenia Bulletin*, 30(2), 459.
- Evins, A. E., Mays, V. K., Rigotti, N. A., Tisdale, T., Cather, C., & Goff, D. C. (2001). A pilot trial of bupropion added to cognitive behavioral therapy for smoking cessation in schizophrenia. *Nicotine & tobacco research*, 3(30), 397-403.
- Evins, A. E., Cather, C., Rigotti, N. A., Freudenreich, O., Henderson, D. C., Olm-Shipman, C. M., et al. (2004). Two-Year Follow-Up of a Smoking Cessation Trial in Patients with Schizophrenia: Increased Rates of Smoking Cessation and Reduction. *Journal of Clinical Psychiatry*, 65(3), 307-11.
- Evins, A. E., Cather, C., Deckersbach, T., Freudenreich, O., Culhane, M. A., Olm-Shipman, C. M., et al. (2005). A double-blind placebo controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. *Journal of Clinical Psychopharmacology*, 25(3), 218-25.
- Evins, A. E., Cather, C., Pratt, S. A., Pachas, G. N., Hoepfner, S. S., Goff, D. C., et al. (2014). Maintenance treatment with varenicline for smoking cessation in patients with schizophrenia and bipolar disorder: a randomized clinical trial. *JAMA*, 311(2), 145-54.
- Ezzati, M., & Lopez, A. D. (2003). Estimates of global mortality attributable to smoking in 2000. *The Lancet*, 362(9387), 847-852.
- Faner, R., Tal-Singer, R., Riley, J. H., Celli, B., Vestbo, J., MacNee, W., et al. (2014). Lessons from ECLIPSE: A review of COPD biomarkers. *Thorax*, 69(7), 666-672.
- Fagerström, K. (2012). Determinants of tobacco use and renaming the FTND to the Fagerström Test for Cigarette Dependence. *Nicotine & tobacco research*, 14(1), 75-78.
- Farsalinos, K. & E., Polosa, R. (2014). Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. *Therapeutic Advances in Drug Safety*, 5(2), 67-86.
- Farsalinos, K. E., Spyrou, A., Tsimopoulou, K., Stefopoulos, C., Romagna, G., & Voudris V. (2014a). Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Sci Rep*, 4, 4133.

- Farsalinos, K. E., Romagna, G., Tsiapras, D., Kyrzopoulos, S., & Voudris, V. (2014b). Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. *International Journal of Environmental Research and Public Health*, 11(4), 4356-4373.
- Farsalinos, K., Cibella, F., Caponnetto, P., Campagna, D., Morjaria, J. B., Battaglia, E., et al. (2016). Effect of continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to electronic cigarettes. *Internal and Emergency Medicine*, 1(10), 1-10.
- Fiore, M. C., Jaen, C. R., Baker, T. B., Bailey, W. C., Benowitz, N., Curry, S. J., et al. (2008). Treating tobacco use and dependence: 2008 update, US Department of Health and Human Services, Public Health Service, *Respiratory care*, 53(9), 1217-22.
- Flanders, W. D., Lally, C. A., Zhu, B. P., Henley, S. J., & Thun, M. J. (2003). Lung cancer mortality in relation to age, duration of smoking, and daily cigarette consumption: results from Cancer Prevention Study II. *Cancer research*, 63(19), 6556-6562.
- Flick, Uwe. (1998/2002/2006). *An Introduction to Qualitative Research* (1st-3rd edition). London: Sage.
- Fogt, D. L., Levi, M. A., Rickards, C. A., Stelly, S. P., & Cooke, W. H. (2016). Effects of acute vaporized nicotine in non-tobacco users at rest and during exercise. *International Journal of Exercise Science*, 9(5), 607-615.
- Foulds, J., Veldheer, S., Yingst, J., Hrabovsky, S., Wilson, S. J., Nichols, T. T., et al. (2015). Development of a questionnaire for assessing dependence on electronic cigarettes among a large sample of ex-smoking E-cigarette users. *Nicotine Tob Res*, 17(2), 186-92.
- Franco, T., Trapasso, S., Puzzo, L., & Allegra, E. (2016). Electronic cigarette: Role in the primary prevention of oral cavity cancer. *Clinical Medicine Insights: Ear, Nose and Throat*. 9, 7-12.
- Filia, S. L., Baker, A. L., Gurvich, C. T., Richmond, R., Lewin, T. J., & Kulkarni, J. (2014). Gender differences in characteristics and outcomes of smokers diagnosed with psychosis participating in a smoking cessation intervention. *Psychiatry Research*, 215(3), 586– 593.
- George, T.P, Ziedonis, D.M., Feingold, A., Pepper, W.T., Satterburg, C.A., Winkel, J., et al. (2000). Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *Am J Psychiatry*, 157, 1835–1842.

- George, T.P., Vessicchio, J.C., Termine, A., Bregartner, T.A., Feingold, A., Rounsaville, B.J., et al. (2002). A placebo-controlled trial of bupropion for smoking cessation in schizophrenia. *Biological Psychiatry*, *52*, 53–61.
- Gallus, S., Zuccaro, P., Colombo, P., Apolone, G., Pacifici, R., Garattini, S., et al. (2006). Effects of new smoking regulations in Italy. *Ann Oncol*, *17*: 346-347.
- Gallus, S., Lugo, A., Colombo, P., Pacifici, R., La Vecchia, C. (2013). Smoking prevalence in Italy 2011 and 2012, with a focus on hand-rolled cigarettes. *Prev Med*, *56*: 314-318.
- Gilbert, H. A. (1965). *Smokeless non-tobacco cigarette* (3,200.819). Retrieved from <http://www.njgasp.org/patents/US3200819>
- Giovenco, D. P., & Delnevo, C. D. (2018). Prevalence of population smoking cessation by electronic cigarette use status in a national sample of recent smokers. *Addictive behaviors*, *76*, 129-134.
- Glasser, A. M., Collins, L., Pearson, J. L., Abudayyeh, H., Niaura, R. S., Abrams, D. B., & Villanti, A. C. (2017). Overview of electronic nicotine delivery systems: a systematic review. *American journal of preventive medicine*, *52*(2), e33-e66.
- Godfrey, C., Parrott, S., Coleman, T., Pound, E. (2005). The cost-effectiveness of the English smoking treatment services: evidence from practice. *Addiction* *100*(2), 70-83.
- Goldberg, J. O. (2010). Successful Change in Tobacco Use in Schizophrenia. *Journal of the American Psychiatric Nurses Association*, *16*(1), 30–35.
- Goldenson, N. I., Kirkpatrick, M. G., Barrington-Trimis, J. L., Pang, R. D., McBeth, J. F., Pentz, M. A., et al. (2016). Effects of sweet flavorings and nicotine on the appeal and sensory properties of e-cigarettes among young adult vapers: Application of a novel methodology. *Drug and alcohol dependence*, *168*, 176-180.
- Goniewicz, M. L., Smith, D. M., Edwards, K. C., Blount, B. C., Caldwell, K. L., Feng, J., al. (2018). Comparison of Nicotine and Toxicant Exposure in Users of Electronic Cigarettes and Combustible Cigarettes. *JAMA Network Open*, *1*(8):e18593
- Gonzalez, A., Zvolensky, M. J., Vujanovic, A. A., Leyro, T. M., & Marshall, E. C. (2008). An evaluation of anxiety sensitivity, emotional dysregulation, and negative affectivity among daily cigarette smokers: relation to smoking motives and barriers to quitting. *Journal of psychiatric research*, *43*(2), 138–147.
- Gorman, G.E. (2005). *Qualitative Research for the Information Professional: A Practical Handbook* (2nd ed.). London: Facet.

- Green, J., Willis, K., Hughes, E., Small, R., Welch, N., Gibbs, L., & Daly, J. (2007). Generating best evidence from qualitative research: The role of data analysis. *Australia and New Zealand Journal of Public Health, 31*(6), 545– 550.
- Guichenez, P., Clauzel, I., Cungi, C., Quantin, X., Godard, P., & Clauzel, A. M. (2007). The contribution of cognitive-behavioural therapies to smoking cessation. *Revue des maladies respiratoires, 24*(2), 171-182.
- Guo, X., Zhai, J., Liu, Z., Fang, M., Wang, B., Wang, C., et al. (2010). Effect of antipsychotic medication alone vs combined with psychosocial intervention on outcomes of early-stage schizophrenia. *Archives of general psychiatry, 67*, 895-904.
- Hahn, B., Ross, T. J., & Stein, E. A. (2006). Neuroanatomical dissociation between bottom–up and top–down processes of visuospatial selective attention. *Neuroimage, 32*(2), 842-853.
- Hahn, B., Harvey, A. N., Concheiro-Guisan, M., Huestis, M. A., Holcomb, H. H., & Gold, J. M. (2013). A Test of the Cognitive Self-Medication Hypothesis of Tobacco Smoking in Schizophrenia. *Biological psychiatry, 74*(6), 436-443.
- Haijma, S. V., Van Haren, N., Cahn, W., Koolschijn, P. C. M., Hulshoff Pol, H. E., & Kahn, R. S. (2013). Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. *Schizophrenia bulletin, 39*(5), 1129-1138.
- Hajek, P., Phillips-Waller, A., Przulj, D., Pesola, F., Myers Smith, K., Bisal, N., et al. (2019). A randomized trial of e-cigarettes versus nicotine-replacement therapy. *New England Journal of Medicine, 380*(7), 629-637.
- Hammersley, M., & Atkinson, P. (2007). *Ethnography: Principles in practice*. New York (NY): Taylor and Francis.
- Harris, J. G., Kongs, S., & Allensworth, D., (2004). Effects of nicotine on cognitive deficits in schizophrenia. *Neuropsychopharmacology, 29*(7), 1378.
- Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. (2016) Can electronic cigarettes help people stop smoking, and are they safe to use for this purpose? *Cochrane Database of Systematic Reviews Issue 9*.
- Hartz, S. M., Pato, C. N., Medeiros, H., Cavazos-Rehg, P., Sobell, J. L., Knowles, J. A., et al. (2014). Comorbidity of severe psychotic disorders with measures of substance use. *JAMA psychiatry, 71*(3), 248-254.
- Hefner, K., Rosenheck, R., Merrel, J., Coffman, M., Valentine, G., & Sofuoglu, M. (2016). E-cigarette use in VA service users with mental health and substance use disorders. *Journal of dual diagnosis, 12*(2), 109-117.

- Hefner, K., Valentine, G., & Sofuoglu, M. (2017). Electronic Cigarettes and Mental Illness: Reviewing the Evidence for Help and Harm Among Those with Psychiatric and Substance Use Disorders. *The American journal on addictions*, 26(4), 306-315.
- Heiberg, I.H., Jacobsen, B.K., Nesvåg, R., Bramness, J.G., Reichborn-Kjennerud, T., Næss, Ø., et al. (2018). Total and cause-specific standardized mortality ratios in patients with schizophrenia and/or substance use disorder. *PLoS ONE* 13(8): e0202028.
- Helen, G. S., Dempsey, D. A., Havel, C. M., Jacob III, P., & Benowitz, N. L. (2017). Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. *Drug and alcohol dependence*, 178, 391-398.
- Hepner, W. L., Ji, L., Reitzel, L. R., Castro, Y., Correa-Fernandez, V., Vidrine, J. I., et al. (2011). The role of prepartum motivation in the maintenance of postpartum smoking abstinence. *Health Psychology*, 30(6), 736-745.
- Hickling L.M., Perez-Iglesias R., McNeill A., Dawkins L., Moxham J., Ruffell T., et al. (2018). A pre-post pilot study of electronic cigarettes to reduce smoking in people with severe mental illness. *Psychological Medicine*, 1–8
- Himelhoch, S., & Daumit, G. (2003). To whom do psychiatrists offer smoking-cessation counseling? *American Journal of Psychiatry*, 160(12), 2228-2230.
- Holloway, I., & Todres, L. (2003). The status of method: flexibility, consistency and coherence. *Qualitative research*, 3(3), 345-357.
- Hon, L. (2003). U.S. Patent 8393331 B2 Electronic Atomization Cigarette, <https://docs.google.com/viewer?url=patentimages.storage.googleapis.com/pdfs/US8393331>.
- Horst, W. D., Klein, M. W., Williams, D., & Werder, S. F. (2005). Extended use of nicotine replacement therapy to maintain smoking cessation in persons with schizophrenia. *Neuropsychiatric disease and treatment*, 1(4), 349-355.
- Howes, O. D., McCutcheon, R., Owen, M. J., & Murray, R. M. (2017). The role of genes, stress, and dopamine in the development of schizophrenia. *Biological psychiatry*, 81(1), 9-20.
- Huang, H., Dong, M., Zhang, L., Zhong, B.L., Ungvari, G.S., Yuan, Z., et al. (2019). Psychopathology and extrapyramidal side effects in smoking and non-smoking patients with schizophrenia: Systematic review and meta-analysis of comparative studies. *Prog Neuropsychopharmacol Biol Psychiatry*, 8(92), 476-482.

- Hughes, J. R., Hatsukami, D. K., Mitchell, J. E., & Dahlgren, L. A. (1986). Prevalence of smoking among psychiatric patients. *The American Journal of Psychiatry*, 143(8), 993-997.
- Hughes, J. R., & Carpenter, M. J. (2006). Does reduction increase future cessation and decrease disease risk? A qualitative review. *Nicotine & Tobacco Research*, 8(6), 739–749.
- Hughes, J.R., Stead, L.F., Lancaster, T. (2007). Antidepressants for smoking cessation. Cochrane database of systematic reviews (Online):CD000031.
- Hunter, A., Murray, R., Asher L., Leonardi-Bee, J. (2018) The Effects of Tobacco Smoking, and Prenatal Tobacco Smoke Exposure, on Risk of Schizophrenia: A Systematic Review and Meta-Analysis. *Nicotine & Tobacco Research*, nty160
- Hummel, K., Brown, J., Willemsen, M. C., West, R., & Kotz, D. (2017). External validation of the Motivation to Stop Scale (MTSS): Findings from the International Tobacco Control (ITC) Netherlands survey. *European Journal of Public Health*, 27(1), 129-134.
- IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.
- Istituto Nazionale di Statistica (ISTAT) (2015). Annuario statistico Italiano 2013. Available at: http://www.istat.it/it/files/2013/12/ASI_2013.pdf. (Accessed December 2, 2017).
- Jardin, B. F., & Carpenter, M. J. (2012). Predictors of quit attempts and abstinence among smokers not currently interested in quitting. *Nicotine & Tobacco Research*, 14(10), 1197-1204.
- Jensen, R. P., Luo, W., Pankow, J. F., Strongin, R. M., & Peyton, D. H. (2015). Hidden formaldehyde in e-cigarette aerosols. *New England Journal of Medicine*, 372(4), 392-394.
- Jiménez-Ruiz, C. A., Masa, F., Miravittles, M., Gabriel, R., Viejo, J. L., Villasante, C., et al. (2001). Smoking characteristics: Differences in attitudes and dependence between healthy smokers and smokers with COPD. *Chest*, 119(5), 1365-1370.
- Jochelson, J., & Majrowski B. (2007). Clearing the Air. Debating Smoke-Free Policies in Psychiatric Units. *King's Fund*.
- Johnson, J. L., Moffat, B., & Malchy, L. (2010). In the shadow of a new smoke free policy: A discourse analysis of health care providers' engagement in tobacco control in community mental health. *International Journal of Mental Health Systems*, 4(1), 23.

- Joossens, L., & Raw, M. (2013). The tobacco control scale 2013 in Europe. Association of European Cancer leagues. 2014. Available at: http://www.europeancancerleagues.org/images/TobaccoControl/TCS_2013_in_Europe_13-03-14_final_1.pdf. (Accessed September 22, 2017).
- Jordan, G., Lutgens, D., Joobar, R., Lepage, M., Iyer, S. N., & Malla, A. (2014). The relative contribution of cognition and symptomatic remission to functional outcome following treatment of a first episode of psychosis. *Journal of clinical psychiatry*, 75(6), e566-572.
- Jubelt, L. E., Barr, R. S., Goff, D. C., Logvinenko, T., Weiss, A. P., & Evins, A. E. (2008). Effects of transdermal nicotine on episodic memory in non-smokers with and without schizophrenia. *Psychopharmacology*, 199(1), 89-98.
- JUUL. (2018). Manufacturing quality: what is JUUL? San Francisco, CA: JUUL Labs, Inc. <https://support.juulvapor.com/home/learn/faqs/manufacturing-quality#materials>. (Accessed June 14, 2018).
- Kalkhoran, S., & Glantz, S. A. (2016). E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *The Lancet Respiratory Medicine*, 4(2), 116-128.
- Kee, C. (2018). Everything you need to know about the JUUL, including the health effects: BuzzFeed News, 2018.
- Keefe, R. S., Goldberg, T. E., Harvey, P. D., Gold, J. M., Poe, M. P., & Coughenour, L. (2004). The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophrenia research*, 68(2-3), 283-297.
- Kelly, D. L., McMahon, R. P., Wehring, H. J., Liu, F., Mackowick, K. M., Boggs, D. L., et al. (2011). Cigarette smoking and mortality risk in people with schizophrenia. *Schizophrenia Bulletin*, 37(4), 832-838.
- Kelly, D. L., Raley, H. G., Lo, S., Wright, K., Liu, F., McMahon, R. P., Heishman, S. J. (2012). Perception of smoking risks and motivation to quit among nontreatment-seeking smokers with and without schizophrenia. *Schizophrenia bulletin*, 38(3), 543–551.
- Keltner, N. L., & Grant, J. S. (2006). Smoke, smoke, smoke that cigarette. *Perspectives in psychiatric cite*, 42(4), 256-266.
- Kendrick, A. H. (2010). Exhaled carbon monoxide devices in smoking cessation: physiology, controversies and equipment. *The buyers' guide to respiratory care products*, 13, 180-189.

- Khantzian, E. J. (1997). The self-medication hypothesis of substance use disorders: A reconsideration and recent applications. *Harvard review of psychiatry*, 4(5), 231-244.
- Khoudigian, S., Devji, T., Lytvyn, L., Campbell, K., Hopkins, R., & O'reilly, D. (2016). The efficacy and short-term effects of electronic cigarettes as a method for smoking cessation: A systematic review and a meta-analysis. *International journal of public health*, 61(2), 257-267.
- King, N., & Horrocks, C. (2010). *Interviews in qualitative research*. Los Angeles: Sage.
- Kishi, T., & Iwata, N. (2015). Varenicline for smoking cessation in people with schizophrenia: systematic review and meta-analysis. *European archives of psychiatry and clinical neuroscience*, 265(3), 259-268.
- Kleine, S. S., & Baker, S. M. (2004). An Integrative review of material possession attachment. *Academy of Marketing Science Review*, (1), 1–39.
- Knowles, S., Planner, C., Bradshaw, T., Peckham, E., Man, M-S., & Gilbody, S. (2016). Making the journey with me: a qualitative study of experiences of a bespoke mental health smoking cessation intervention for service users with serious mental illness. *BMC Psychiatry*, 16:193.
- Kobayashi, M., Ito, H., Okumura, Y., Mayahara, K., Matsumoto, Y., & Hirakawa, J. (2010). Hospital Readmission in First-Time Admitted Patients with Schizophrenia: Smoking Patients Had Higher Hospital Readmission Rate Than Non-Smoking Patients. *The International Journal of Psychiatry in Medicine*, 40(3), 247–257.
- Kopelowicz, A., Liberman, R. P., & Zarate, R. (2002). Psychosocial treatments for schizophrenia. In Nathan, P., E., & Gorman, J., M. (Eds.), *A guide to treatments that Work*, 2nd Edition (pp. 201–229). New York: Oxford University Press
- Kotov, R., Guey, L. T., Bromet, E. J., & Schwartz, J. E. (2010). Smoking in schizophrenia: Diagnostic specificity, symptom correlates, and illness severity. *Schizophrenia bulletin*, 36(1), 173-181.
- Kotz, D., Brown, J., & West, R. (2013). Predictive validity of the Motivation To Stop Scale (MTSS): A single-item measure of motivation to stop smoking. *Drug and Alcohol Dependence*, 128(1-2), 15-19.
- Kowalczyk, W. J., Wehring, H. J., Burton, G., Raley, H., Feldman, S., Heishman, S. J., & Kelly, D. L. (2017). Predictors of the Perception of Smoking Health Risks in Smokers With or Without Schizophrenia. *Journal of dual diagnosis*, 13(1), 29–35.

- Kreyenbuhl, J., Buchanan, R. W., Dickerson, F. B., & Dixon, L. B. (2010). The schizophrenia patient outcomes research team (PORT): Updated treatment recommendations 2009. *Schizophrenia bulletin*, 36(1), 94-103.
- Kumari, V., & Postma, P. (2005). Nicotine use in schizophrenia: The self medication hypotheses. *Neuroscience & Biobehavioral Reviews*, 29(6), 1021-1034.
- La Vecchia, C., Franceschi, S., & Levi, F. (2003). Epidemiological research on cancer with a focus on Europe. *European Journal of Cancer Prevention*, 12(1), 5-14.
- Lasser, K., Boyd, J. W., Woolhandler, S., Himmelstein, D. U., McCormick, D., & Bor, D. H. (2000). Smoking and mental illness: a population-based prevalence study. *JAMA*, 284(20), 2606-2610.
- Lawn, S. J., Pols, R. G., & Barber, J. G. (2002). Smoking and quitting: a qualitative study with community-living psychiatric clients. *Social Science & Medicine*, 54(1), 93-104.
- Lawrence, D., Mitrou, F., & Zubrick, S. R. (2009). Smoking and mental illness: results from population surveys in Australia and the United States. *BMC public health*, 9(1), 285.
- Lawrence, D., Hancock, K.J., Kisely, S. (2013). The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population-based registers. *BMJ* 346: f2539
- Lawler R (2018). Vaporization startup Pax Labs introduces Juul, its next-gen e-cigarette. Techcrunch.com 2015. <https://techcrunch.com/2015/04/21/pax-juul/> (Accessed June 14, 2018).
- Lawn, S. J., Pols, R. G., & Barber, J. G. (2002). Smoking and quitting: a qualitative study with community-living psychiatric clients. *Social science & medicine*, 54(1), 93-104.
- Lee, J., Green, M. F., Calkins, M. E., Greenwood, T. A., Gur, R. E., Gur, R. C., et al. (2015). Verbal working memory in schizophrenia from the consortium on the genetics of schizophrenia (COGS) study: the moderating role of smoking status and antipsychotic medications. *Schizophrenia Research*, 163(0), 24–31.
- Lee, Y. O., & Kim, A. E. (2015). 'Vape shops' and 'E-Cigarette lounges' open across the USA to promote ENDS. *Tobacco control*, 24(4), 410-412.
- Lenzenweger, M. F. (2006). Schizotypy: an organizing framework for schizophrenia research. *Current Directions in Psychological Science*, 15(4), 162-166.

- Leonard, S., & Adams, C. E. (2006). Smoking cessation and schizophrenia. *American Journal of Psychiatry*, 163(11), 1877.
- Levy, D. T., Yuan, Z., Luo, Y., & Abrams, D. B. (2017). The relationship of E-cigarette use to cigarette quit attempts and cessation: insights from a large, nationally representative US survey. *Nicotine & Tobacco Research*, 1-9.
- Lindson-Hawley, N., Aveyard, P., & Hughes, J. R. (2012). Reduction versus abrupt cessation in smokers who want to quit. *Cochrane Database of Systematic Reviews*, 14(11).
- Ling, P. M., & Glantz, S. A. (2005). Tobacco industry consumer research on socially acceptable cigarettes. *Tobacco Control*, 14(5), e3-e3.
- Lugo, A., Ascitto, R., Pacifici, R., Colombo, P., La Vecchia, C., & Gallus, S. (2015). Smoking in Italy 2013-2014, with a focus on the young. *Tumori Journal*, 101(5), 529-534.
- Lundbäck, B., Lindberg, A., Lindström, M., Rönmark, E., Jonsson, A. C., Jönsson, E., et al. (2003). Not 15 but 50% of smokers develop COPD? Report from the Obstructive Lung Disease in Northern Sweden studies. *Respiratory medicine*, 97(2), 115-122.
- MacDonald, A. W., & Chafee, M. V. (2006). Translational and developmental perspective on N-methyl-D-aspartate synaptic deficits in schizophrenia. *Development and Psychopathology*, 18(3), 853-876.
- Majeed, B. A., Weaver, S. R., Gregory, K. R., Whitney, C. F., Slovic, P., Pechacek, T. F., et al. (2017). Changing perceptions of harm of e-cigarettes among US adults, 2012–2015. *American journal of preventive medicine*, 52(3), 331-338.
- Mann-Wrobel, M. C., Bennett, M. E., Weiner, E. E., Buchanan, R. W., & Ball, M. P. (2011). Smoking history and motivation to quit in smokers with schizophrenia in a smoking cessation program. *Schizophrenia research*, 126(1-3), 277-283.
- Manzella F., Maloney, S. E., & Taylor, G. T. (2015). Smoking in schizophrenic patients: A critique of the self-medication hypothesis. *World J Psychiatry*, 5 (1), 35–46.
- Manzoli, L., Flacco, M. E., Ferrante, M., La Vecchia, C., Siliquini, R., Ricciardi, W. (2017). Cohort study of electronic cigarette use: effectiveness and safety at 24 months. *Tobacco control*, 26(3), 284-292.
- McCloughen, A. (2003). The association between schizophrenia and cigarette smoking: a review of the literature and implications for mental health nursing practice. *International journal of mental health nursing*, 12(2), 119-129.

- McChargue, D. E., Gulliver, S. B., & Hitsman, B. (2002). Would smokers with schizophrenia benefit from a more flexible approach to smoking treatment? *Addiction*, *97*(7), 785-793.
- McEvoy, J. P., Johnson, J., Perkins, D., Lieberman, J. A., Hamer, R. M., Keefe, R. S. (2006). Insight in first-episode psychosis. *Psychological medicine*, *36*(10), 1385-1393.
- McEwen, A. (2014). Standard Treatment Programme: A Guide to Behavioural Support for Smoking Cessation. National Centre for Smoking Cessation and Training. (2 nded.).
- McEwan A, McRobbie H. (2016). Electronic cigarettes: a briefing for stop smoking services.
- McRobbie, H., Bullen, C., Hartmann-Boyce, J., Hajek, P. (2014). Electronic cigarettes for smoking cessation and reduction (Review). *The Cochrane database of systematic reviews*, *12*, 17.
- McRobbie, H., Phillips, A., Goniewicz, M. L., Smith, K. M., Knight-West, O., Przulj, D., et al. (2015). Effects of switching to electronic cigarettes with and without concurrent smoking on exposure to nicotine, carbon monoxide, and acrolein. *Cancer Prevention Research*, *8*(9), 873-878.
- Mendrek, A., Bourque, J., Dubé, A., Lakis, N., & Champagne, J. (2012). Emotion processing in women with schizophrenia is menstrual cycle phase and affective valence dependent: an fMRI study. *ISRN psychiatry*, *2012*, 656274
- Meurk, C., Ford, P., Sharma, R., Fitzgerald, L., & Gartner, C. (2016). Views and preferences for nicotine products as an alternative to smoking: A focus group study of people living with mental disorders. *International journal of environmental research and public health*, *13*(11), 1166.
- Mexal, S., Berger, R., Logel, J., Ross, R. G., Freedman, R., & Leonard, S. (2010). Differential regulation of $\alpha 7$ nicotinic receptor gene (CHRNA7) expression in schizophrenic smokers. *Journal of molecular neuroscience*, *40*(1-2), 185-195.
- Michie, S., Richardson, M., Johnston, M., Abraham, C., Francis, J., Hardeman, W., et al. (2013). The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Annals of behavioral medicine*, *46*(1), 81-95.
- Miller, B. J., Wang, A., Wong, J., Paletta, N., & Buckley, P. F. (2017). E-cigarette use in schizophrenia: prevalence and attitudes. *Annals of Clinical Psychiatry*, *29*(1), 4-10.

- Mitchell, A. J., Vancampfort, D., De Hert, M., & Stubbs, B. (2015). Do people with mental illness receive adequate smoking cessation advice? A systematic review and meta-analysis. *General hospital psychiatry*, 37(1), 14-23.
- Moerer-Urdahl, T., & Creswell, J. W. (2004). Using transcendental phenomenology to explore the “ripple effect” in a leadership mentoring program. *International Journal of Qualitative Methods*, 3(2), 1-28.
- Moheimani, R. S., Bhetraratana, M., Yin, F., Peters, K. M., Gornbein, J., Araujo, J. A., et al. (2017). Increased cardiac sympathetic activity and oxidative stress in habitual electronic cigarette users: implications for cardiovascular risk. *JAMA cardiology*, 2(3), 278-284.
- Mooney, M. E., & Sofuoglu, M. (2006). Bupropion for the treatment of nicotine withdrawal and craving. *Expert Review of Neurotherapeutics*, 6(7), 965-81.
- Moustakas, C. (1994). *Phenomenological research methods*. Thousand Oaks, CA: Sage.
- Myles, N., Newall, H. D., Curtis, J., Nielssen, O., Shiers, D., & Large, M. (2012). Tobacco use before, at, and after first-episode psychosis: a systematic meta-analysis. *The Journal of clinical psychiatry*, 73(4), 468–475.
- National Institute of Mental Health (2016). Schizophrenia. Retrieved from <https://www.nimh.nih.gov/health/topics/schizophrenia/index.shtml> (Accessed May 27, 2019).
- National Institute for Health and Care Excellence. (2011). Public health guidance scope: Tobacco: Harm-reduction approaches to smoking. London.
- National Institute for Health and Care Excellence. (2013). Public Health Guideline 45 Tobacco: Harm-reduction approaches to smoking. London.
- Nuechterlein, K. H., Green, M. F., Kern, R. S., Baade, L. E., Barch, D. M., Cohen, J. D., et al. (2008). The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *American Journal of Psychiatry*, 165(2), 203-213.
- Norman, D. A. (2004). *Emotional design: Why we love (or hate) everyday things*. New York: Basic Books.
- Novelli, M., Lopes Cardozo, M. T., & Smith, A. (2017). The 4Rs framework: Analyzing education’s contribution to sustainable peacebuilding with social justice in conflict-affected contexts.

- Novick, D., Haro, J. M., Suarez, D., Vieta, E., & Naber, D. (2009). Recovery in the outpatient setting: 36-month results from the Schizophrenia Outpatients Health Outcomes (SOHO) study. *Schizophrenia Research*, 108, 223-230.
- Nutt, D. J., Phillips, L. D., Balfour, D., Curran, H. V., Dockrell, M., Foulds, J., et al. (2016). E-cigarettes are less harmful than smoking. *Lancet*, 387(10024), 1160-1162.
- O'Brien, B., Knight-West, O., Walker, N., Parag, V., & Bullen, C. (2015). E-cigarettes versus NRT for smoking reduction or cessation in people with mental illness: secondary analysis of data from the ASCEND trial. *Tobacco induced diseases*, 13(1), 5.
- Ohtani, T., Levitt, J. J., Nestor, P. G., Kawashima, T., Asami, T., Shenton, M. E., et al. (2014). Prefrontal cortex volume deficit in schizophrenia: a new look using 3 T MRI with manual parcellation. *Schizophrenia research*, 152(1), 184-190.
- Olfson, M., Gerhard, T., Huang, C., Crystal, S., & Stroup, T. S. (2015). Premature mortality among adults with schizophrenia in the United States. *JAMA psychiatry*, 72(12), 1172-1181.
- Osborn, D.P., Levy, G., Nazareth, I., Petersen, I., Islam, A., King, M.B. (2007). Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Research Database. *Arch Gen Psychiatry*, 64(2), 242-9.
- OSSFAD. (2008). Osservatorio Droga Alcol e Fumo. Linee guida cliniche per promuovere la cessazione dell'abitudine al fumo.
- OSSFAD. (2012). Osservatorio Droga Alcol e Fumo. Rapporto annuale sul fumo.
- OSSFAD. (2016). Osservatorio Droga Alcol e Fumo. Rapporto annuale sul fumo.
- OSSFAD. (2018). Osservatorio Droga Alcol e Fumo. Rapporto annuale sul fumo.
- Osuna, E., Pérez-Carrión, A., Pérez-Cárceles, M. D., & Machado, F. (2018). Perceptions of health professionals about the quality of communication and deliberation with the patient and its impact on the health decision making process. *Journal of public health research*, 7(3).
- Owen, M. J., Sawa, A., & Mortensen, P.B. (2016). Schizophrenia. *Lancet*, 388, 86-97.
- Padgett, D. K. (2008). *Qualitative methods in social work research* (Vol. 36). Sage Publications.

- Pankow, J. F., Kim, K., McWhirter, K. J., Luo, W., Escobedo, J. O., Strongin, R. M., et al. (2017). Benzene formation in electronic cigarettes. *PLoS ONE*, *12*(3).
- Parikh, V., Kutlu, M. G., & Gould, T. J. (2016). nAChR dysfunction as a common substrate for schizophrenia and comorbid nicotine addiction: Current trends and perspectives. *Schizophrenia research*, *171*(1-3), 1-15.
- Partti, K., Vasankari, T., Kanervisto, M., Perälä, J. (2015). Lung function and respiratory diseases in people with psychosis: Population-based study. *The British Journal of Psychiatry*. *207*(1), 37-45.
- Patton MQ. (200). Qualitative research and evaluation methods. 3rd Sage Publications; Thousand Oaks, CA.
- Pawlikowska, T., Zhang, W., Griffiths, F., van Dalen, J., & van der Vleuten, C. (2012). Verbal and non-verbal behavior of doctors and patients in primary care consultations—How this relates to patient enablement. *Patient education and counseling*, *86*(1), 70-76.
- Peckham, E., Brabyn, S., Cook, L., Tew, G., & Gilbody, S. (2017). Smoking cessation in severe mental ill health: what works? An updated systematic review and meta-analysis. *BMC psychiatry*, *17*(1), 252.
- Pearson, J. L., Hitchman, S.C., Brose, L.S., Bauld, L., Glasser, A.M, Villanti, A.C et al. (2018). Recommended core items to assess e-cigarette use in population-based surveys. *Tobacco Control* *27*, 341-346.
- Pepper, J. K., Emery, S. L., Ribisl, K. M., Rini, C. M., & Brewer, N. T. (2015). How risky is it to use e-cigarettes? Smokers' beliefs about their health risks from using novel and traditional tobacco products. *Journal of behavioral medicine*, *38*(2), 318–326.
- Perez Mata, M., Ahmed-Kristensen, S., Brockhoff, P. B., & Yanagisawa, H. (2017). Investigating the influence of product perception and geometric features. *Research in Engineering Design*, *28*(3), 357–379.
- Perfetti, T. A., & Rodgman, A. (2013). *The chemical components of tobacco and tobacco smoke*. New York: NY CRC press
- Polosa, R., Morjaria, J. B., Caponnetto, P., Campagna, D., Russo, C., Alamo, A., et al. (2014a). Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study. *Internal and emergency medicine*, *9*(5), 537-546.
- Polosa, R., Morjaria, J., Caponnetto, P., Caruso, M., Strano, S., Battaglia, E., et al. (2014b). Effect of smoking abstinence and reduction in asthmatic smokers

switching to electronic cigarettes: Evidence for harm reversal. *International journal of environmental research and public health*, 11(5), 4965-4977.

Polosa, R., Morjaria, J. B., Caponnetto, P., Caruso, M., Campagna, D., Amaradio, M. D., et al. (2016a). Persisting long term benefits of smoking abstinence and reduction in asthmatic smokers who have switched to electronic cigarettes. *Discovery medicine*, 21(114), 99-108.

Polosa, R., Morjaria, J. B., Caponnetto, P., Prosperini, U., Russo, C., Pennisi, A., et al. (2016b). Evidence for harm reduction in COPD smokers who switch to electronic cigarettes. *Respiratory research*, 17(1), 166.

Polosa, R., Cibella, F., Caponnetto, P., Maglia, M., Prosperini, U., Russo, C., et al. (2017). Health impact of E-cigarettes: a prospective 3.5-year study of regular daily users who have never smoked. *Scientific reports*, 7(1), 13825.

Potvin, S., Bourque, J., Durand, M., Lipp, O., Lalonde, P., Stip, E., ... Mendrek, A. (2013). The neural correlates of mental rotation abilities in cannabis-abusing patients with schizophrenia: an fMRI study. *Schizophrenia research and treatment*, 543842.

Poulsen, L. H., Osler, M., Roberts, C., Due, P., Damsgaard, M. T., & Holstein, B. E. (2002). Exposure to teachers smoking and adolescent smoking behaviour: analysis of cross-sectional data from Denmark. *Tobacco control*, 11(3), 246-251.

Pratt, S. I., Sargent, J., Daniels, L., Santos, M. M., & Brunette, M. (2016). Appeal of electronic cigarettes in smokers with serious mental illness. *Addictive behaviors*, 59, 30-34.

Prochaska, J. O., & DiClemente, C. C. (1983). Stages and processes of self-change of smoking: toward an integrative model of change. *Journal of Consulting and Clinical Psychology*, 51, 390-395.

Prochaska, J. J. (2011). Smoking and mental illness-breaking the link. *New England Journal of Medicine*, 365 (3), 196-198.

Pulvers, K., Emami, A. S., Nollen, N. L., Romero, D. R., Strong, D. R., Benowitz, N. L., et al. (2016). Tobacco consumption and toxicant exposure of cigarette smokers using electronic cigarettes. *Nicotine and Tobacco Research*, 20(2), 206-214.

Purcell, S. M., Moran, J. L., Fromer, M., Ruderfer, D., Solovieff, N., & Roussos, P., et al. (2014). A polygenic burden of rare disruptive mutations in schizophrenia. *Nature*, 506 (7487), 185-90.

Rabin, R., & Charro, F. D. (2001). EQ-SD: a measure of health status from the EuroQol Group. *Annals of medicine*, 33(5), 337-343.

- Radding B (2015). Pax Juul: the iPhone of e-cigs? *Mens Fit* 2015
- Rae, J., Pettey D., Aubry, T., Stol, J. (2015) Factors Affecting Smoking Cessation Efforts of People with Severe Mental Illness: A Qualitative Study. *Journal of Dual Diagnosis*, 11(1), 42-49.
- Randolph, C., Tierney, M. C., Mohr, E., & Chase, T. N. (1998). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *Journal of clinical and experimental neuropsychology*, 20(3), 310-319.
- Rass, O., Pacek, L. R., Johnson, P. S., & Johnson, M. W. (2015). Characterizing use patterns and perceptions of relative harm in dual users of electronic and tobacco cigarettes. *Experimental and clinical psychopharmacology*, 23(6), 494–503.
- Ratschen, E., Britton, J., Doody, G. A., Leonardi-Bee, J., & McNeill, A. (2009). Tobacco dependence, treatment and smoke-free policies: a survey of mental health professionals' knowledge and attitudes. *General hospital psychiatry*, 31(6), 576-582.
- Rees, V. W., Kreslake, J. M., Wayne, G. F., O'Connor, R. J., Cummings, K. M., & Connolly, G. N. (2012). Role of cigarette sensory cues in modifying puffing topography. *Drug and alcohol dependence*, 124(1-2), 1–10.
- Richardson, G., & Manca, A. (2004). Calculation of quality adjusted life years in the published literature: a review of methodology and transparency. *Health economics*, 13(12), 1203-1210.
- Riley, B. P., Makoff, A., Mogudi-Carter, M., Jenkins, T., Williamson, R., Collier, D., et al. (2000). Haplotype transmission disequilibrium and evidence for linkage of the CHRNA7 gene region to schizophrenia in Southern African Bantu families. *American journal of medical genetics*, 96 (2), 196-201.
- Richtel, M. A. T. T. (2014). Selling a poison by the barrel: liquid nicotine for e-cigarettes. *New York Times*, 23.
- Roberts, E., Eden Evins, A., McNeill, A., & Robson, D. (2016). Efficacy and tolerability of pharmacotherapy for smoking cessation in adults with serious mental illness: a systematic review and network meta-analysis. *Addiction*, 111(4), 599-612.
- Robson, D., & Potts, J. (2014). Smoking cessation and mental health: A briefing for front-line staff.

- Robson, D. & McEwen, A. (2018) Smoking cessation and smoke free policies: Good practice for mental health services. *National Centre for Smoking Cessation and Training (NCSCT)*.
- Royal College of Physicians, Royal College of Psychiatrists. Smoking and mental health. London, RCP, 2013.
- Royal College of Physicians, Royal College of Psychiatrists. The prescribing of varenicline and vaping (electronic cigarettes) to patients with severe mental illness. London, RCP, 2016.
- Russo, C., Cibella, F., Caponnetto, P., Campagna, D., Maglia, M., Frazzetto, E et al. (2016). Evaluation of post cessation weight gain in a 1-year Randomized Smoking Cessation Trial of Electronic Cigarettes. *Scientific reports*, 6, 18763.
- Russell, M. A. H. (1974). Realistic goals for smoking and health: A case for safer smoking. *The Lancet*. 1, 254-258
- Sacco, K. A., Termine, A., Seyal, A., Dudas, M. M., Vessicchio, J. C., Krishnan-Sarin, S., et al. (2005). Effects of cigarette smoking on spatial working memory and attentional deficits in schizophrenia: involvement of nicotinic receptor mechanisms. *Archives of general psychiatry*, 62(6), 649-659.
- Saha, S., Chant, D., & McGrath, J. (2007). A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Archives of general psychiatry*, 64, 1123-1131.
- Šagud, M., Mihaljević-Peleš, A., Mück-Šeler, D., Pivac, N., Vuksan-Ćusa, B., Brataljenović, T., et al. (2009). Smoking and schizophrenia. *Psychiatria Danubina*, 21(3), 371-375.
- Sanford, Z., Goebel, M. D., & Lynne, J. (2014). E-cigarettes: an up to date review and discussion of the controversy. *West Virginia Medical Journal*, 110(4), 10-5.
- Schneider, C. E., White, T., Hass, J., Geisler, D., Wallace, S. R., Roessner, V., et al. (2014). Smoking status as a potential confounder in the study of brain structure in schizophrenia. *Journal of psychiatric research*, 50, 84-91.
- Schifferstein, H. N. J., & Zwartkuis-Pelgrim, E. P. H. (2008). Consumer-product attachment: Measurement and design implications. *International Journal of Design*, 2(3), 1-14.
- Shahab, L., Goniewicz, M. L., Blount, B. C., Brown, J., McNeill, A., Alwis, K. U., et al. (2017). Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: a cross-sectional study. *Annals of internal medicine*, 166(6), 390-400.

- Sharma, R., Wigginton, B., Meurk, C., Ford, P., & Gartner, C. E. (2017a). Motivations and limitations associated with lapin among people with mental illness: A qualitative analysis of Reddit discussions. *International journal of environmental research and public health*, 14 (1), 7.
- Sharma, R., Gartner, C. E., Castle, D. J., & Mendelsohn, C. P. (2017b). Should ween courage smokers with severe mental illness to switch to electronic cigarettes? *Australian & New Zealand Journal of Psychiatry*, 51(7), 663-664.
- Siegel, R. L., Jacobs, E. J., Newton, C. C., Feskanich, D., Freedman, N. D., Prentice, R. L., et al. (2015). Deaths due to cigarette smoking for 12 smoking-related cancers in the United States. *JAMA internal medicine*, 175(9), 1574-1576.
- Siru, R., Hulse, G. K., & Tait, R. J. (2009). Assessing motivation to quit smoking in people with mental illness: a review. *Addiction*, 104(5), 719-733.
- Sleight, V. J. (2016). A brief history of the electronic cigarette. *J Lung Pulm Respir Res*. 3(5), 1-2.
- Smith, P. H., Mazure, C. M., & McKee, S. A. (2014). Smoking and mental illness in the US population. *Tobacco control*, 23 (e2), e147-e153.
- Smith, R. C., Warner-Cohen, J., Matute, M. (2005). Effects of nicotine nasal spray on cognitive function in schizophrenia. *Neuropsychopharmacology*. 31, 637–643.
- Sokal, J., Messias, E., Dickerson, F.B., Kreyenbuhl, J., Brown, C., Goldberg, R.W., et al., (2004). Comorbidity of medical illnesses among adults with serious mental illness who are receiving community psychiatric services. *J. Nerv. Ment. Dis.* 192(6), 421–427.
- Spindle, T. R., Hiler, M. M., Breland, A. B., Karaoghlanian, N. V., Shihadeh, A. L., & Eissenberg, T. (2016). The influence of a mouthpiece-based topography measurement device on electronic cigarette user's plasma nicotine concentration, heart rate, and subjective effects under directed and ad libitum use conditions. *Nicotine & Tobacco Research*, 19(4), 469-476.
- Spring, B., Pingitore, R., & McChargue, D. E. (2003). Reward value of cigarette smoking for comparably heavy smoking schizophrenic, depressed, and non patient smokers. *American Journal of Psychiatry*, 160, 316-322.
- Song, F., Raftery, J., Aveyard, P., Hyde, C., Barton, P., & Woolacott, N. (2002). Cost-effectiveness of pharmacological interventions for smoking cessation: a literature review and a decision analytic analysis. *Medical Decision Making*, 22(1), 26-37.

- Stead, L. F., Perera, R., Bullen, C., Mant, D., Hartmann-Boyce, J., Cahill, K., et al. (2012) Nicotine replacement therapy for smoking cessation. *The Cochrane Database of Systematic Reviews*, CD000146.
- St. Helen, G. S., Dempsey, D. A., Havel, C. M., Jacob III, P., & Benowitz, N. L. (2017). Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. *178*, 391-398.
- Steinberg, M. B., Zimmermann, M. H., Delnevo, C. D., Lewis, M. J., Shukla, P., Coups, E. J., & Foulds, J. (2014). E-cigarette versus nicotine inhaler: comparing the perceptions and experiences of inhaled nicotine devices. *Journal of general internal medicine*, *29*(11), 1444-1450.
- Stephens, W. E. (2018). Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. *Tobacco control*, *27*(1), 10.
- Strauss, A., & Corbin, J. (1998). *Basics of qualitative research*. Thousand Oaks: Sage.
- Streck, J. M., Bergeria, C. L., Parker, M. A., Davis, D. R., DeSarno, M., Sigmon, S. C., Higgins, S. T. (2018). Response to reduced nicotine content cigarettes among smokers with chronic health conditions. *Preventive medicine reports*, *12*, 321–329.
- Stringhini, S., Carmeli, C., Jokela, M., Avendaño, M., Muennig, P., Guida, F., et al. (2017). Socioeconomic status and the 25× 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 17 million men and women. *The Lancet*, *389* (10075), 1229-1237.
- Strongin R. M. (2019). E-Cigarette Chemistry and Analytical Detection. Annual review of analytical chemistry (Palo Alto, Calif.), *12*(1), 23–39.
- Suzuki, T., Remington, G., Mulsant, B. H., Uchida, H., Rajji, T. K., Graff-Guerrero, A., et al. (2012). Defining treatment-resistant schizophrenia and response to antipsychotics: a review and recommendation. *Psychiatry research*, *197*, 1-6.
- Szołtysek-Bołdys, I., Sobczak, A., Zielińska-Danch, W., Bartoń, A., Koszowski, B., & Kośmider, L. (2014). Influence of inhaled nicotine source on arterial stiffness. *Przegląd Lekarski*, *71*(11), 572-575.
- Tajima-Pozo, K., de Castro Oller, M. J., Lewczuk, A., & Montañes-Rada, F. (2015). Understanding the direct and indirect costs of patients with schizophrenia. *F1000 Research*, *4*, 182.

- Tan, A. S., & Bigman, C. A. (2014). E-cigarette awareness and perceived harmfulness: prevalence and associations with smoking-cessation outcomes. *American journal of preventive medicine*, 47(2), 141–149.
- Taylor, G., McNeill, A. & Girling, A. (2014). Change in mental health after smoking cessation: systematic review and meta-analysis. *BMJ*, (vol. 348).
- Tidey, J. W., Rohsenow, D. J., Kaplan, G. B., & Swift, R. M. (2005). Cigarette smoking topography in smokers with schizophrenia and matched non-psychiatric controls. *Drug and Alcohol Dependence*, 80 (2), 259-265.
- Timothy, H.R., Walker, D.M., Mullen, D., Johnson, T.J., Ford, E.W. (2017). Trends in E-Cigarette Awareness and Perceived Harmfulness in the U.S. *American Journal of Preventive Medicine*, 52(3) 339-346.
- Tobacco Atlas. The Tobacco Atlas. 5th ed. Atlanta, GA: American Cancer Society; 2015. Available at: [http:// www.tobaccoatlas.org/](http://www.tobaccoatlas.org/). (Accessed June 18, 2018).
- Trainor, K., Leavey, G. (2017). Barriers and facilitators to smoking cessation among people with severe mental illness: a critical appraisal of qualitative studies. *Nicotine Tob Res*, 19(1),14–23.
- Tran, E., Rouillon, F., Loze, J., Casadebaig, F., Philippe, A., Vitry, F. and Limosin, F. (2009), Cancer mortality in patients with schizophrenia. *Cancer*, 115: 3555-3562.
- Tramacere, I., Gallus, S., Fernandez, E., Zuccaro, P., Colombo, P., & La Vecchia, C. (2009). Medium-term effects of the Italian smoke-free legislation: findings from four annual population-based surveys. *Journal of Epidemiology & Community Health*, 63 (7), 559-562.
- Truth Initiative. *What is JUUL?* Washington, DC: Truth Initiative, 2018. (Accessed June 13, 2018).
- Tsoi, D. T., Porwal, M., & Webster, A. C. (2013). Interventions for smoking cessation and reduction in individuals with schizophrenia. *The Cochrane Database of Systematic Reviews*, 2.
- Tsuda, Y., Saruwatari, J., Yasui-Furukori, N. (2014). Meta-analysis: the effects of smoking on the disposition of two commonly used antipsychotic agents, olanzapine and clozapine. *BMJ Open*, 4:e004216.
- Twyman, L., Bonevski, B., Paul, C., Bryant, J (2014). Perceived barriers to smoking cessation in selected vulnerable groups: A systematic review of the qualitative and quantitative literature. *BMJ Open*, 4(12).

- Ulin, P. R., Robinson, E. T. & Tolley, E. E. (2004). *Qualitative methods in public health: a field guide for applied research*, Wiley. com.
- US Department of Health and Human Services: Atlanta, GA: Centers for Disease Control and Prevention, (2004) *The health consequences of smoking: a report of the surgeon general*. Office of the Surgeon General (US), Office on Smoking and Health (US).
- Ussher, M., Kakar, G., Hajek, P., West, R. (2016) Dependence and motivation to stop smoking as predictors of success of a quit attempt among smokers seeking help to quit. *Addict. Behav*, 53, 175–180.
- Van Erp, T. G. M., Preda, A., Nguyen, D., Faziola, L., Turner, J., Bustillo, J., et al. (2014). Converting positive and negative symptom scores between PANSS and SAPS/SANS. *Schizophrenia research*, 152(1), 289-294.
- Vansickel, A. R., Cobb, C. O., Weaver, M. F., & Eissenberg, T. E. (2010). A clinical laboratory model for evaluating the acute effects of electronic “cigarettes”: nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiology and Biomarkers & Prevention*, 19(8), 1945-1953.
- Viegi, G., Pedreschi, M., Baldacci, S., Chiaffi, L., Pistelli, F., Modena, P., et al. (1999). Prevalence rates of respiratory symptoms and diseases in general population samples of North and Central Italy. *The International Journal of Tuberculosis and Lung Disease*, 3(11), 1034-1042.
- Volk, D. W., Austin, M. C., Pierri, J. N., Sampson, A. R., & Lewis, D. A. (2000). Decreased glutamic acid decarboxylase67 messenger RNA expression in a subset of prefrontal cortical γ -aminobutyric acid neurons in subjects with schizophrenia. *Archives of general psychiatry*, 57 (3), 237-245.
- Walker, E. F., Grimes, K. E., Davis, D. M., & Adina, J. (1993). Child hood precursors of schizophrenia: facial expressions of emotion. *The American Journal of Psychiatry*, 150, 1654-1660.
- Walker, E. F., Savoie, T., & Davis, D. (1994). Neuromotor precursors of schizophrenia. *Schizophrenia bulletin*, 20(3), 441-451.
- Walker, E., Kestler, L., Bollini, A., & Hochman, K. (2004). Schizophrenia: etiology and course. *Annual Review Psychology*, 55, 401-430.
- Walker, E., & Tessner, K. (2008). Schizophrenia. *Perspectives on Psychological Science*, 3(1), 30–37.
- Wang, Y-Y., Wang, S., Zheng, W., Zhong, B-L., Ng, C.H., Ungvarie, G.S., Wang, C-X., Li, X-H., Xiang, Y-T. (2019) Cognitive functions in smoking and non-smoking

- patients with schizophrenia: A systematic review and meta-analysis of comparative studies. *Psychiatry Research*, 272, 155-163.
- Wagener, T. L., Siegel, M., & Borrelli, B. (2012). Electronic cigarettes: achieving a balanced perspective. *Addiction*, 107(9), 1545-1548.
- Wailoo, A., Davis, S., & Tosh, J. (2010). The Incorporation of Health Benefits in Cost Utility Analysis Using the EQ-5D: A Report by the Decision Support Unit. *Sheffield: School of Health and Related Research, University of Sheffield*.
- Watt, N. F. (1974). *Childhood and adolescent roots of schizophrenia*. In D. Ricks, A. Thomas & M. Roll (Eds.), *Life history research in psychopathology* (Vol. 3). Minneapolis: University of Minnesota Press
- Wedzicha, J. A., & Donaldson, G. C. (2003). Exacerbations of chronic obstructive pulmonary disease. *Respiratory care*, 48 (12), 1204-1215.
- Warner K. E. & Burns D. M. (2003). Hardening and the hard-core smoker: concepts, evidence, and implications. *Nicotine and Tobacco Res*, 5, 37-48.
- Weiner, E., Buchholtz, A., Coffay, A., Liu, F., McMahon, R. P., Buchanan, R. W., et al. (2011). Varenicline for smoking cessation in people with schizophrenia: a double-blind randomized pilot study. *Schizophrenia research*, 129(1), 94-95.
- West, R., McEwen, A., Bolling, K., & Owen, L. (2001). Smoking cessation and smoking patterns in the general population: a 1-year follow-up. *Addiction*, 96(6), 891-902.
- West, R., & Jarvis, M. (2005). Tobacco smoking and mental disorder. *Italian Journal of Psychiatry and Behavioural Science*, 15, 10-17.
- West, R., Hajek, P., Stead, L., & Stapleton, J. (2005). Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction*, 100(3), 299-303.
- West, R. (2009). The multiple facets of cigarette addiction and what they mean for encouraging and helping smokers to stop. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, 6 (4), 277-283.
- Wiiium, N., Breivik, K., &Wold, B. (2006). The relationship between smoker role models and intentions to smoke among adolescents. *Journal of Youth and Adolescence*, 35(4), 549-560.
- White, A.R., Rampes, H., Liu, J.P., Stead, L.F., Campbell, J. (2014). Acupuncture and related interventions for smoking cessation. *Cochrane Database of Systematic Reviews*, Issue 1.

- Williams, J. M., Gandhi, K. K., Lu, S. E., Kumar, S., Shen, J., Foulds, J., et al. (2010a). Higher nicotine levels in schizophrenia compared with controls after smoking a single cigarette. *Nicotine & tobacco research*, 12 (8), 855-859.
- Williams, J. M., Steinberg, M. L., Zimmermann, M. H., Gandhi, K. K., Stipelman, B., Budsock, P. D., et al. (2010b). Comparison of two intensities of tobacco dependence counseling in schizophrenia and schizoaffective disorder. *Journal of substance abuse treatment*, 38(4), 384-393.
- Williams, J. M., Gandhi, K. K., Lu, S. E., Kumar, S., Steinberg, M. L., Cottler, B., & Benowitz, N. L. (2011). Shorter interpuff interval is associated with higher nicotine intake in smokers with schizophrenia. *Drug and alcohol dependence*, 118(2-3), 313–319.
- Winterbourne, S. (2012). *Preventing future physical morbidity and premature mortality in first-episode psychosis patients: an economic evaluation of smoking cessation interventions*. London, UK: MSc Thesis.
- Witkiewitz, K., & Marlatt, G. A. (2004). Relapse prevention for alcohol and drug problems: that was Zen, this is Tao. *American Psychologist*, 59 (4), 224.
- Woodberry, K. A., Giuliano, A. J., & Seidman, L. J. (2008). Premorbid IQ in schizophrenia: a meta-analytic review. *American Journal of Psychiatry*, 165, 579-587.
- World Health Organization, Cabral de Mello, M., Bornemann, T. H., Levav, I., Leff, J., Patel, V., & Saraceno, B. (2001). *Mental health: Call for Action by World Health Ministers*. World Health Organization. Retrieved from http://www.who.int/entity/mental_health/media/en/249.pdf. (Accessed May 27, 2018).
- World Health Organization (WHO) (2003): *WHO Framework Convention on Tobacco Control*. Geneva: WHO Press.
- World Health Organization (WHO) (2008). World Health Statistics 2008. www.who.int/whosis/whostat/2008/en. (Accessed April 1, 2018).
- World Health Organization, (WHO) 2010). The International Classification of Diseases (ICD-10) Classification of Mental and Behavioural Disorders.
- World Health Organization (WHO) (2012). WHO global report: Mortality attributable to tobacco.2012:392. http://whqlibdoc.who.int/publications/2012/9789241564434_eng.Pdf. (Accessed January 1, 2016).
- World Health Organization (WHO) (2017). *World No Tobacco Day 2017: Beating tobacco for health, prosperity, the environment and national development*.

<http://www.who.int/mediacentre/news/releases/2017/no-tobacco-day/en/>.
(Accessed 25, November 2017).

- World Health Organization (WHO) (2018). WHO global report: Mortality attributable to tobacco. 2012:392. <http://www.who.int/gho/database/en/>. (Accessed February 11, 2018).
- Yann, S. & Marina, R. (2008). Genetics of nicotinic acetylcholine receptors: Relevance to nicotine addiction. *Biochemical Pharmacology*, 75, 323–333.
- Yan, X. S., & D’Ruiz, C. (2015). Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. *Regulatory Toxicology and Pharmacology*, 71(1), 24-34.
- York, L.N. (1997). *A phenomenological investigation of cigarette smoking in persons with severe and persistent mental illness*. Doctoral dissertation, Saint Louis University, St Louis.
- Zemann A. (2011) Smoke chemistry. In: Bernhard D, ed. Cigarette Smoke Toxicity. Weinheim: Wiley-VCH Verlag & Co. KGaA; pp. 55–64.
- Zenzes, M. T. (2000). Smoking and reproduction: gene damage to human gametes and embryos. *Human Reproduction Update*, 6 (2), 122-131
- Zhang, X. Y., Chen, D. C., Xiu, M. H., Haile, C. N., He, S. C., Luo, X., et al. (2013). Cigarette smoking, psychopathology and cognitive function in first-episode drug-naïve patients with schizophrenia: a case-control study. *Psychological medicine*, 43 (8), 1651-1660.
- Zhou, X., Nonnemaker, J., Sherrill, B., Gilseman, A. W., Coste, F., & West, R. (2009). Attempts to quit smoking and relapse: factors associated with success or failure from the ATTEMPT cohort study. *Addictive behaviors*, 34(4), 365-373.
- Zhu, S. H., Sun, J. Y., Bonnevie, E., Cummins, S. E., Gamst, A., Yin, L., & Lee, M. (2014). Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tobacco control*, 23(3), 3-9.
- Zhu, S. H., Zhuang, Y. L., Wong, S., Cummins, S. E., & Tedeschi, G. J. (2017). E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. *The BMJ*, 358, j3262.
- Ziedonis, D. M., Kosten, T. R., Glazer, W. M., & Frances, R. J. (1994). Nicotine dependence and schizophrenia. *Hospital & Community Psychiatry*, 45(3), 204-206.

Ziedonis, D. M., & George, T. P. (1997). Schizophrenia and nicotine use: report of a pilot smoking cessation program and review of neurobiological and clinical issues. *Schizophrenia Bulletin*, 23 (2), 247-254.

Ziedonis, D., Hitsman, B., Beckham, J. C., Zvolensky, M., Adler, L. E., Audrain-McGovern, J., et al. (2008). Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine and tobacco research*, 10(12), 1691–1715.

APPENDICES

APPENDIX 1

Ethics approval, qualitative study

JE/SF

24 October 2016

Pasquale Caponnetto
Research Student
Institute for Social Marketing
University of Stirling
Stirling FK9 4LA

UNIVERSITY of
STIRLING 

NHS, Invasive or Clinical Research (NICR)
Committee

Room G10
Pathfoot Building
University of Stirling
Stirling FK9 4LA

Tel: +44 (0) 1786 467390
Email: nicr@stir.ac.uk

Dear Pasquale

Traditional cigarette and e-cigarette use in adult smokers with schizophrenia motivated and not motivated to quit: a qualitative study of users' perceptions and implications for smoking cessation or reduction
NICR 2016 – Paper No. 01

Thank you for your email in response to the NICR correspondence dated 20 September 2016 which included the following attachments:

- Cover note
- SREC Application V2
- Participant Information Sheet V2
- Participant Consent Form V2

I am pleased to advise that your study has been granted approval, and wish you and your team all the best. Although there are some grammatical errors in your Patient Information Leaflets, we note that these will be translated into Italian so we have disregarded the errors. However, please ensure that NICR receives copies of the final versions.

May I remind you of the need to inform NICR (nicr@stir.ac.uk) prior to making any amendments to this protocol, or any changes to the duration of the project and provide notification of study completion. A site file of all documents related to the research should be maintained throughout the life of the project, and kept up to date at all times. The site file template can be found on the NICR webpage at:
<http://www.stir.ac.uk/research/integritygovernanceethics/researchethics/formsandguidance/>

Please bear in mind that your study could be audited for adherence to research governance and research ethics protocols.

NICR 2016 – Paper No.01
Please quote this number on all correspondence

Yours sincerely



Dr Josie Evans
(Depute Chair)
Cc Prof. Linda Bauld, Supervisor

APPENDIX 2

Information sheet for patients, qualitative study

I would like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done. Please take the time to read through the information here and contact me to discuss any questions you may have, or if anything is not clear. This information sheet tells you the purpose of the study and what will happen to you if you take part.

What is the purpose of the study?

I'm a researcher undertaking doctoral studies at the University of Stirling, UK and I working on smoking behaviour and schizophrenia. This is a project to (1) examine sensations of e-cigarettes compared to traditional cigarettes; (2) examine sensations of approved smoking cessation aids; (3) examine the appeal for initiating and using e-cigarettes as smoking cessation/reduction method; (4) examine the appeal for initiating and using approved smoking cessation aids as smoking cessation/reduction method

Why I'm invited?

As part of this research I would like to talk to people with schizophrenia who have been selected by their clinicians at Schizophrenia center for participation at this project and invite you to complete an interview.

What will happen if I take part?

Your will be invited to take part in a face to face interview which will be completed during office hours. The interview will take about 60 minutes. Participation is voluntary and you can withdraw at any time either before, during or after the interview. The interview will be audio-recorded and will be conducted in conversational in style.

Will the data you collect be confidential?

What you tells me will be completely confidential unless they tell me something that makes me concerned for their safety or that of someone else. I will follow ethical and legal practice for the protection of your data. No-one except the research team will find out what you say and your participation in the study will not affect your care in the Centre at all. Interview data will be stored anonymously and held securely on a University password protected computer that can only be accessed by authorised members of the research team. You will not be named or identified in any way in the results from the study such as reports or presentations. The results will be a series of information on **traditional cigarette and e-cigarette use derived by** interviews recorded and transcribed verbatim.

Before any research goes ahead it has to be approved by a Research Ethics Committee. This project has been approved by the University of Stirling Research Ethics Committee.

What happens if I have some questions?

If you have any questions please speak to me, your teacher or a Professor from the University using the contact details below.

I hope you are happy to participate. If you are, you do **NOT** need to do anything. If you have any questions or concerns about any aspect of the study please contact Dr Pasquale Caponnetto (78, S.Sofia street, 95100 Catania, telephone: 095 3781537 email: pasquale.caponnetto@stir.ac.uk) or Prof Riccardo Polosa (78, S.Sofia street 95100 Catania, telephone: 095 3781583 email: polosa@unict.it). If you would like to speak to someone independent of the research team at the University of Stirling – please please contact Professor Jayne Donaldson, Dean of Faculty of Health Sciences & Sport (telephone: 0044 1786 466345 email: jayne.donaldson@stir.ac.uk).

If you're happy to take part in an interview, please tick each box below

- | |
|---|
| a) I am interested in taking part in this study. <input type="checkbox"/> |
| b) I am happy for the researcher to contact me and arrange <input type="checkbox"/> a time to discuss what would be involved prior to arranging an interview |

Signed.....Date.....

Many thanks for your time,

Pasquale Caponnetto,

Phd Students, Stirling University

APPENDIX 3

Participant consent form, qualitative study

Version 2 DATE 01.10.2016

Please refer to the study information sheet or contact the research team (0953781537 pasquale.caponnetto@stir.ac.uk) if you would like further details about the study or if you have any questions.

Please note that your participation is entirely voluntary and you are free to withdraw at any time, without giving any reason. The information you provide will be confidential and will be securely stored. Only the research team will have access to it and your name will not be in any outputs from the research.

This research study involves:

- One 60-minute face to face interview.

Please **initial the boxes and sign your name** if you agree to take part in this research

| | |
|--|--------------------------|
| I agree to take part in the research | <input type="checkbox"/> |
| I confirm that I have read and understood the information sheet. If I had any questions, I have discussed these with the researcher and these have been answered satisfactorily. | <input type="checkbox"/> |
| I understand that my participation is voluntary and I am free to withdraw at any time without giving a reason. | <input type="checkbox"/> |
| I understand that the information I provide may be used in publications, reports and presentations | <input type="checkbox"/> |
| I understand that any information that can identify me will not appear in publications, reports or presentations and that my name will be anonymised | |

Name of Participant

Date

Signature

APPENDIX 4

Structured interview

Interview schedule/topic guide for smokers with schizophrenia

INSTRUCTIONS FOR RESEARCH WORKER Aims

(1) Examine perceptions of e-cigarettes compared to traditional cigarettes; (2) examine perceptions of approved cessation aids; (3) examine the appeal for initiating and using e-cigarettes as smoking cessation/reduction tool; (4) examine the appeal for initiating and using approved cessation aids as smoking cessation/reduction tool

a) Introduction and consent

Aim: To introduce the research, clarify the content of the interview, explain confidentiality and gain consent.

The interview will last up to an hour with an additional fifteen minutes to complete consent and respondent demographic data.

- Introduce yourself
- Introduce research
- Participation is voluntary and participant can withdraw at any time either before, during or after the interview
- Explain confidentiality (confidential unless participant report anything which may indicate harm to themselves or others)
- Recording (to gain accurate record of discussion, allow interviewer to focus on what respondent is saying, only research team will hear it)
- Length (about 60 minutes with breaks if needed)
- Nature of discussion (conversational in style with specific topics to be addressed)
- Place of interview (need for private space to conduct the interview)
- Reporting and data storage (no-one identified in final report, data stored securely under

Data Protection legislation – can only be used for purpose collected by law, e.g. transcripts kept in locked cabinets, not shared with anyone outside research team)

- Address any questions
- Gain written consent

b) Sociodemographic form

Aim: To gain background information about the interviewee.

INTERVIEW QUESTIONS

Introduction (5-10 minutes)

START RECORDING Aim: To find out a little bit about the person and to help build rapport in the interview

Tell me a little bit about yourself

Prompts:

- o Tell me a little bit about yourself and your experiences
- o Tell me a little bit about your smoking history
- o Story of their mental health experience

Section 1: e-cigarettes and traditional cigarettes (7 - 12 mins)

Aim: To find out about the individual's perceptions of e-cigarettes compared to traditional cigarettes.

What do you think about classic cigarette? (e.g., taste, satisfaction, cost, impact on health.....)

What do you think about the electronic cigarette? (e.g., taste, satisfaction, cost, impact on health, impact on quitting.....)

Prompt:

- o can you tell me what you feel similar?
- o can you tell me what you feel different?

Section 2: approved smoking cessation aids (7 - 12 mins)

Aim: To find out about the individual's perceptions of approved smoking cessation aids.

What treatments do you know about that help people stop smoking?

Prompt:

- o can you tell me what you think about NRT?
- o can you tell me what you think about bupropion?
- o can you tell me what you think about varenicline?

Section 3: e-cigarettes smoking cessation/reduction (7 - 12 mins)

Aim: To find out about the appeal of e-cigarettes (initiation and as a smoking cessation/reduction tool)

Would you use an electronic cigarette to quit tobacco smoking?

Please explain why

Would you use an electronic cigarette to reduce tobacco smoking?

Please explain why

Section 4: approved smoking cessation aids cessation/reduction (7 - 12 mins)

Aim: To find out about the appeal of using approved smoking cessation aids

Would you use NRT to quit tobacco smoking?

Please explain why

Would you use NRT to reduce tobacco smoking?

Please explain why

Would you use Bupropion to quit tobacco smoking? ask 2 separate question

Please explain why

You would use Bupropion to reduce tobacco smoking?

Please explain why

Would you use Varenicline to quit tobacco smoking? ask 2 separate question

Please explain why

You would use Varenicline to reduce tobacco smoking?

Please explain why

Ask for any other comments.

End of interview. Thank respondent and close interview.

APPENDIX 5

Example of transcript and coding

(NINO, MASCHIO, ETÀ 38)

Se le va mi parla un pò di lei?

Ma che programma è questo?

Buonasera, mi chiamo Nino ed ho 38 anni mi trovo in trattamento per esattamente un intoppo nella vita considerando che io sia stato sempre un ragazzo molto vivo allegro gioviale e soprattutto con tanta voglia di fare per una serie di eventi correlati a dei lutti, non probabilmente non molto elaborati mi sono trovato ad avere un periodo un po' negativo.

Considerato il fatto che io nella mia vita ho avuto sempre delle basi che sono quelle della famiglia quindi non parliamo del fatto che mio padre possa essere stato un grande imprenditore o che mio padre poteva essere un muratore o che mio padre poteva essere quello che era e mia mamma viceversa, comunque una solidale famiglia porta il benessere di un ragazzo nel senso che se hai un problema sai a chi rivolgerti se stai male sai a chi rivolgerti.

Considerando il fatto che mia madre mi ha insegnato che poi a un certo punto i problemi dovevo risolverli da solo cioè mi ha insegnato se ti senti male ti nni vai dal medico, nel senso però un ragazzo con certezze ben assolute quindi per un certo punto queste mie certezze ben assolute, quindi per un certo punto queste mie certezze sono crollate.

Possono essere quelle affettive, quelle possono essere, sono state anche lavorative perché mi trovavo in una situazione lavorativa molto favorevole che improvvisamente è diventata stop. Diciamo che non è stato non proprio favorevole però come un ragazzo che ha sempre vissuto la sua vita pienamente cerca di riprendersi la sua vita in un moto che sia comunque soddisfacente anche per il proseguo della sua vita. Per quanto concerne il fumare se v'interessa veramente, non m'interessa fumare, se v'interessa veramente non m'interessa fumare, però in questo momento è semplicemente una piccola valvola di sfogo che non è avere una ragazza o non avere un gruppo di amici, ma la cosa importante è essere un ragazzo solido forte e sicuro di sè.

Poi tutto il resto viene da solo gli amici le fidanzate tutto quello che concerne la vita nel senso proprio quando tu sei sereno tranquillo poi tutto il resto viene da solo senza problemi, poi la gente si avvicina senza che tu te ne accorga.

Raccontami un po' la tua storia da fumatore *Ma dottore io non ho mai fumato in modo eccessivo nel senso ho iniziato a fumare a 16 anni quando sono stato insieme con gli amici, poi in questo periodo ho fumato un po' di più perché ho avuto una valvola di sfogo.*

Raccontami un pò della tua esperienza nell'ambito della salute mentale

Allora rispetto al mio equilibrio psichico mi trovo meglio, il problema sa qual è nasce dal fatto che per un ragazzo che non ha mai avuto un problema del genere di vita, avere un problema e non averne un supporto familiare adeguato e trovare un medico che ti sappia sopportare per come un ragazzo vuole essere sopportato non è stato neanche semplice. Perché il primo medico dice passerà, il secondo medico dice fa passare un po' di tempo, poi passano gli anni fondamentalmente non ti riprendi e quanto meno non è che non ti riprendi perché fisicamente poi automaticamente scattano le difese di automeccanismo però conoscendo il tuo corpo sai che lavorare al 20 per cento rispetto al 100 per cento. Che tu non vuoi dare e per un ragazzo cioè per lo meno per la mia personalità non è propriamente buono quindi trovare un medico di riferimento, non è proprio semplicissimo nel senso se tu non hai grosse aspettative nella vita vai da un medico, vivi giorno per giorno, poi quello che ti succede succede, io non sono fatto proprio così quindi se tu hai un medico che ti sappia riprendere ha senso, cioè ovvio il passato non lo puoi riprendere o quanto meno devi avere un futuro che sia degno del passato o per lo meno degno per te, cioè non per gli altri che probabilmente se ne stanno fregando.

Quali sono i tuoi pensieri rispetto alle sigarette classiche?

E' veramente stupida (risponde alla domanda sulla sigaretta classica) non ha nessun senso è semplicemente un palliativo che non ha assolutamente un senso logico cioè la nicotina è la nicotina, non c'è niente che fare cioè io ho provato la sigaretta elettronica ma la nicotina è la nicotina. Ah io stavo parlando avevo capito sigaretta elettronica. La sigaretta classica mi da soddisfazione.

La sigaretta classica è importante perché è vero la nicotina, il tabacco fanno certo come posso dire... devi andare dal dentista ogni sei mesi

Cioè devi curare quell'aspetto che non è proprio facile della sigaretta, no? E quindi però sicuramente nel momento di benessere io non voglio utilizzare sigarette perché non ne avevo nessun motivo ma nel momento di malessere è un piccolo palliativo. Diciamo che ho scoperto nella vita l'affetto della propria madre, o l'affetto in generale della famiglia, a un certo punto della vita è mancato e quindi mi sono reso conto cioè nel senso un affetto di una famiglia compatta può portarti tante cose positive e quindi ti può evirare tante altre cose negative tipo la sigaretta, nel senso la sigaretta, nel senso la sigaretta, in questo momento è un palliativo perché non hai uno sfogo ben preciso cioè nel senso in questo momento stai lavorando, potrei tornare in ufficio ma non è più per come lo immaginavo io .

Quindi se non lavori e ti senti diciamo, non ti senti potente cioè questo voglio dire se non ti senti con le palle quadrate, tendi a fumare, io questo l'ho visto su di me nella mia gioventù mi sentivo con le palle quadrate quindi non avevo bisogno di fumare.

Un senso cioè, un senso probabilmente lo poteva avere lo spinello, come amico mio a livello di amicizia tipo tra me e la sigaretta di per sé a meno che c'è gente che ha il vizio ma fondamentalmente non lo puoi creare.

Vabbè il costo di una sigaretta non è così disabilitante cioè voglio dire 5 euro a settimana 5-10 euro non è che sono una cosa pazzesca

Si il costo di una sigaretta di 5-10 euro a settimana non è così esorbitante voglio dire 5-10 euro a settimanali puoi spendere per la sigaretta, ne puoi spendere anche di più, però voglio dire parliamo della sigaretta come esempio da seguire nella mia vita, è un esempio sbagliato. Ha problemi finiamo? domani? no prego.

Cosa pensa della sigaretta classica in termini di impatto sulla salute?

Non penso faccia tanto bene alla salute, l'incidenza tumorale è abbastanza alta e anche le malattie cardiovascolari sono molto frequenti! Sono informato su questo perché ho avuto esperienza con mio padre e so che più o meno nel 70% dei casi, il cancro è dovuto al fumo, oltre il fattore ereditario o altro.

Cosa ne pensi della sigaretta elettronica?

La sigaretta elettronica è una grandissima stupidaggine, un palliativo ed è anche più costosa della sigaretta normale, l'unica cosa positiva forse è che per la salute è un po' meglio, e che è più economica rispetto alle sigarette, ma la verità è che si dovrebbe smettere e basta!

Per quanto riguarda il gusto della sigaretta elettronica cosa ne pensi?

La sigaretta ha il sapore della sigaretta mentre la sigaretta elettronica ha sapore di fragola o di cocco ecc. Se tu devi fumare fumi la sigaretta normale altrimenti non fumi!

Cosa pensi del grado di soddisfazione della sigaretta elettronica?

Non mi dà soddisfazione, per chi fuma una boccata di sigaretta normale è una cosa differente!

Quali somiglianze percepisci tra sigarette normali e sigarette elettroniche?

nessuna!

E quali differenze?

Quella normale è sigaretta, quella elettronica è un'altra cosa... si capisce!

Quali trattamenti conosci per smettere di fumare?

Il primo? La volontà!

Non conosco altre cure

Cosa pensi dei sono i sostitutivi nicotinici?

Ho avuto esperienze indiretta riguardo a questi! Per me la sigaretta è come una droga perché la nicotina ti crea dipendenza e i cerotti che hanno un impatto non superiore al 50% sul fisico, per un fumatore occasionale non servirebbe neanche ma basterebbe avere una distrazione; mentre per il fumatore abituale la quantità di nicotina del cerotto non può sopperire al bisogno di nicotina dell'organismo. Secondo me chi vuole smettere di fumare o lo fa dopo aver preso un grosso spavento tipo un TIA o un infarto cardiaco, oppure deve essere spinto dalla propria volontà! Cerotti o sigarette elettroniche hanno poca influenza e non hanno nessun senso!

Potresti dirmi cosa pensi del bupropione?

No! Non so cosa sia

Potresti dirmi cosa pensi della vareniclina?

Non ho mai sentito parlarne

E' un farmaco che agisce sulle stesse aree che sono occupate dalla nicotina, ma non è nicotina ed è forse il più efficace tra i farmaci per smettere di fumare!

Vorresti utilizzare la sigaretta elettronica per smettere di fumare?

No!

Perché

Non mi soddisfa

Vorresti utilizzare la sigaretta elettronica per ridurre?

No!

Perché

Non mi soddisfa

Vorresti utilizzare i sostitutivi nicotinici per smettere di fumare?

No!

Se volessi smettere di fumare inizierei a fumare il tabacco per due motivazioni: innanzitutto perché il tabacco macchia le dita e questa è una cosa brutta dal punto di vista estetico e potrebbe essere un incentivo a smettere; da un punto di vista pratico poi è più complicato da utilizzare perché bisogna comprare tabacco, cartine e assemblare la sigaretta e questo potrebbe portare a far stancare.

Vorresti utilizzare i sostitutivi nicotinici per ridurre?

No!

Perché

Non servono. I cerotti soddisfano metà del bisogno di nicotina e sono buoni per fumatori occasionali e non per i fumatori regolari perché non soddisfano il loro bisogno nicotinic.

Vorresti utilizzare Bupropione per smettere di fumare?

No!

Perché

L'unica cura è la forza di volontà

Vorresti utilizzare Bupropione per ridurre?

No!

Perché

L'unica cura è la forza di volontà

Vorresti utilizzare Vareniclina per smettere di fumare?

No!

Perché

L'unica cura è la forza di volontà

Vorresti utilizzare Vareniclina per ridurre?

No!

Perché

L'unica cura è la forza di volontà

Hai altri commenti o altre cose da dire rispetto all'argomento?

La sigaretta elettronica ti permette di avere solo la sensazione della boccata di sigaretta... però se prendiamo un campione di 100 fumatori 10 fumano la sigaretta elettronica e 90 la sigaretta normale...

Per esempio in un periodo come questo per un ragazzo che frequenta il centro per la cura della schizofrenia, la sigaretta è l'unico passatempo reale e quindi secondo

me, per quanto mi riguarda, questa vita da questo punto di vista non aiuta, perché quando avevo una vita normale e frequentavo i miei amici un pacchetto di sigarette mi durava due giorni, quindi anche la costrizione in un luogo crea abitudini che tu nella vita non ha mai avuto. Probabilmente se tu vivi all'aria aperta, sei più sereno e sei felice e non hai bisogno di doverti organizzare la giornata, giorno per giorno... quindi secondo me il centro per la cura della schizofrenia non aiuta!

E' tutto?

Si!

Ti ringrazio!

NINO, MALE, AGED 38

If you want, tell me a little bit about yourself.

But what is this program?

Good evening my name is Nino and I'm 38 years old, I'm in treatment for exactly a hitch in life considering that I've always been a very happy, jovial, and most of all like to do for a series of mournful events, probably not not very elaborate I found to have a somewhat negative period.

Considering the fact that I always had bases in my life that are family ones so we do not talk about the fact that my father may have been a great businessman or that my father could be a bricklayer or that my father could be what he was and My mom vice-versa, however, a solid family brings a boy's well-being in the sense that if you have a problem you know who to turn to you if you're sick you know whom to turn. Considering that my mother taught me that then at some point I had to solve the problems on their own, that is, she taught me if you feel bad about you go to the doctor in the sense, but a guy with certain assurances so for a while these my, so certain assurances therefore for some time these my certainties have collapsed.

They may be those affective, they may be, they were also working because I was in a very favorable working situation that suddenly stopped. We say that it was not quite favorable, however, as a boy who has always lived his life fully tries to recover his life in a motion that is still satisfactory even for the continuation of his life. With

regard to smoking if you really care, I'm not interested in smoking, if I'm really interested, I'm not interested in smoking, but at this time it's just a small relief valve that's not having a girlfriend or having a group of friends but the important thing is to be a strong and strong guy of sure of himself.

Then everything else comes from friends alone, friends all about life in the right sense, when you are quite calm then everything else comes alone without any problems, then people get close without you noticing it.

Tell me a little bit about your smoking history

But doctor I have never smoked excessively, in the sense I started to smoke when I was 16 with my friends, then this time I smoked a bit more because I had a vent valve.

Tell me a little bit about story of your mental health experience

So, with respect to my psychic balance, I find myself better, the problem is what is the fact that for a boy who has never had a life-style problem, have a problem and do not have adequate family support and find a doctor who knowing how to endure how a boy wants to be born was not even simple. Because the first doctor says it will pass, the second doctor says it takes some time, then the years basically do not take you back and at least it's just that you do not resume it because physically then automatically take the defences of self-mechanics but knowing your body, you know you work at 20 percent compared to 100 percent. That you do not want to give and for a guy ie at least for my personality is not really good so find a referral doctor, it's not very simple in the sense if you do not have big expectations in life go to a doctor, live day to day, then what happens to you happens, I'm not doing it so so, if you have a doctor who knows how to resume it makes sense, ie obviously you cannot resume the past or at least you have a future that is worthy of the past or for the least worthy of you, that is, not for others who are likely to be frigging.

What do you think about classic cigarette?

It's really stupid (he is answering the question about classic cigarette) does not make any sense is just a palliative that has absolutely no logical meaning that nicotine is nicotine, there is nothing to do, I tried the electronic cigarette but the Nicotine is

nicotine. Ah I was talking about electronic cigarette. Classic cigarette give me satisfaction.

The classic cigarette is important because nicotine is true, tobacco is certain as I can say ... you have to go to the dentist every six months

That is, you have to cure that aspect that is not easy for the cigarette, right? And then surely at the moment of well-being I do not want to use cigarettes because I had no reason but at the time of illness is a small palliative.

Let's say that I have discovered in the life the affection of one's mother, or the general affection of the family, at some point in life is missing and so I realized that in the sense a companion's affection can bring you many positive things So you can see so many other negative things like cigarettes, in the sense of the cigarette, in the sense of the cigarette, at this time it is a palliative because you do not have a very precise venture ie in the sense at this time you are working, I could go back to the office but not Is more about how I imagined it. So if you do not work and you feel we say, you do not feel powerful ie that I mean if you do not feel yourself with square balls, you smoke, I saw this on me in my youth I felt myself with square balls so I did not need to smoke.

One sense, that is, a sense probably could have the spinel, as a friend of mine in the kind of friendship between me and the cigarette by itself unless there are people who have the vice but basically you cannot create it.

Well the cost of a cigarette is not so disabling ie it means 5 euros a week, 5-10 euro is not a crazy thing

The cost of a cigarette of 5-10 euros a week is not so exorbitant I mean 5-10 euros per week you can spend on the cigarette, you can spend even more, but I mean we talk about cigarettes as an example to follow in my Life, it is a wrong example. It has problems we end up? Tomorrow? No thanks.

What do you think of classic cigarette in terms of impact on health?

It is dangerous for health, cancer incidence is high in smokers, and cardiovascular disease is also very common in smokers! I am informed about this because I have had experience with my father and I know that more or less in 70% of cases is due to smoke beyond the hereditary factor or other.

What do you think about the electronic cigarette?

The electronic cigarette is a very stupid, is a palliative and is also more expensive than normal cigarettes, the only positive thing is that health is a bit better but the truth is that you should quit enough!

What do you think about the taste of the electronic cigarette?

The cigarette has the cigarette flavor while the electronic cigarette has strawberry or coconut flavor and so on. If you have to smoke, smoke the normal cigarette otherwise it will not smoke!

What do you think about the satisfaction of the electronic cigarette?

It does not give me satisfaction, for those who smoke a normal cigarette puff is a different thing!

Can you tell me what you feel similar between normal cigarettes and electronic cigarettes?

None!

Can you tell me what you feel different?

The normal one is cigarette, the electronic one is another thing ... you understand!

What treatments do you know about that help people stop smoking?

The first one? The willpower!

I don't know other treatment

Can you tell me what you think about nicotine replacement therapy?

I had indirect experiences about these! For me the cigarette is like a drug because nicotine adds to you, for an occasional smoker the patches that have an impact no more than 50% on the physical, are not effective, but it would be enough to have a distraction; While for the regular smoker the amount of nicotine in the patch cannot overcome the need for nicotine in the body. In my opinion, anyone who wants to quit smoking or does so after taking a big scare like a TIA or a heart attack, or has to be driven by his own will! Nicotine patches or e-cigarettes have little influence and do not make any sense!

Can you tell me what you think about bupropion?

No! I don't know what is.

Can you tell me what you think about varenicline?

No, I ever heard of varenicline?

It is a drug that acts on the same areas that are occupied by nicotine, but it is not nicotine and is perhaps the most effective drug to stop smoking!

Would you use an electronic cigarette to stop smoking tobacco?

No!

Please explain why

It does not give me satisfaction

Would you use and electronic cigarette to reduce tobacco smoking?

No!

Please explain why

It does not give me satisfaction

Would you use NRT to quit tobacco smoking?

No!

Please explain why

If I want to quit smoking I would start smoking hand rolled tobacco for two reasons: first of all, because the tobacco spots your fingers and this is a bad thing from the aesthetic point of view and it could be an incentive to stop; from a practical point of view it is more complicated to use because you need to buy tobacco, map and assemble the cigarette and this could make you tired.

Would you use NRT to reduce tobacco smoking?

No!

Please explain why

They are not effective. The patches satisfy half of your nicotine needs and are good for occasional smokers and not for regular smokers, because it cannot satisfy their nicotine needs

Would you use Bupropion to quit tobacco smoking?

No!

Please explain why

The only therapy is the willpower

Would you use Bupropion to reduce tobacco smoking?

No!

Please explain why

The only therapy is the willpower

Would you use Varenicline to quit tobacco smoking?

No!

Please explain why

The only therapy is the willpower

Would you use Varenicline to reduce tobacco smoking?

No!

Please explain why

The only therapy is the willpower

Do you have any other comments?

The electronic cigarette allows you to have only the feel of the cigarette mouth ... but if we take a sample of 100 smokers, 10 smoke the electronic cigarette and 90 the normal cigarette ...For example, at a time like this for a boy treated in a schizophrenia center, cigarette is the only real pastime and so in my opinion,

schizophrenia center from this point of view does not help because when I had a normal life, and attended my friends, a packet of cigarettes duration was about two days, so also constraint in a place creates habits that you have never had in life. Probably if you live in the open air, you are more serene and you are happy and you do not need to organize your day, day after day ... so I think the schizophrenia center does not help!

Is it all?

Yes!

Thank you!

| Nodes | | Sources | References |
|----------------------------|--|---------|------------|
| age initiation | | 1 | 1 |
| bpr | | 1 | 2 |
| cost | | 1 | 2 |
| experience | | 1 | 2 |
| health | | 1 | 2 |
| intention to use | | 1 | 2 |
| mental illness ans smoking | | 1 | 1 |
| nrt | | 1 | 3 |
| quit | | 1 | 3 |
| reduce | | 1 | 3 |
| satisfaction | | 1 | 3 |
| similar different | | 1 | 1 |
| Social context | | 1 | 1 |
| taste | | 1 | 1 |
| var | | 1 | 1 |
| why to start | | 1 | 1 |

Intervista Nino tradotta satisfaction

<Internals\Intervista Nino tradotta> - 5 3 references coded [2,33% Coverage]

Reference 1 - 0,37% Coverage

Classic cigarette give me satisfaction

Reference 2 - 0,96% Coverage

It does not give me satisfaction, for those who smoke a normal cigarette puff is a different thing!

Reference 3 - 1,00% Coverage

electronic cigarette to stop smoking tobacco?

No!

Please explain why

It does not give me satisfaction

APPENDIX 6

Ethics approval, quantitative study

JE/SF

27 September 2017

Dr P Caponnetto
Institute for Social Marketing
Faculty of Health Sciences & Sport
University of Stirling
Stirling FK9 4LA

UNIVERSITY of
STIRLING 

NHS, Invasive or Clinical Research (NICR)
Committee

Room G10
Pathfoot Building
University of Stirling
Stirling FK9 4LA

Tel: +44 (0) 1786 467390
Email: nicr@stir.ac.uk

Dear Pasquale

**Role of an electronic cigarettes in smoking displacement in smokers with schizophrenia:
a prospective 3-month pilot study (SchizEcig-P).
NICR 16/17 – Paper No.75**

Thank you for your email of 18 September 2017 which included the following attachments:

- Covering letter
- Approval of Expedited Amendment
- Informed Consent Version 8.17
- Healthcare Provider Contact Record
- Study Protocol – Final
- IRAS Version 2
- IRAS Pg 31 signed

I am pleased to advise that your study has been granted approval, and wish you and your team all the best.

May I remind you of the need to inform NICR (nicr@stir.ac.uk) prior to making any amendments to this protocol, or any changes to the duration of the project and provide notification of study completion. A site file of all documents related to the research should be maintained throughout the life of the project, and kept up to date at all times. The site file template can be found on the NICR webpage at:

<http://www.stir.ac.uk/research/integritygovernanceethics/researchethics/formsandguidance/>

Please bear in mind that your study could be audited for adherence to research governance and research ethics protocols.

NICR 16/17 – Paper No.75
Please quote this number on all correspondence

Yours sincerely



Dr Josie Evans
(Depute Chair)

APPENDIX 7

Health care provider contact record, quantitative study

Participant ID:

Provider/s Contacted (Name/address/phone/email):

Date of Contact

Confirm the following eligibility criteria

Diagnosis

No relapse to hospitalization within the past 3 months

No change in anti-psychotic treatment within the last month

Smokers \geq 20 cigarettes day

Not motivated to quit smoking

Confirm the participant does not meet the following exclusion criteria

Myocardial infarction of angina pectoris within the past 3 months or current poorly controlled asthma

Use of nicotine replacement therapy or other smoking cessation therapies within the last 3 months

Pregnancy or breastfeeding

APPENDIX 8

Flyer, quantitative study

CERCHIAMO VOLONTARI PER UN PROGETTO DI RICERCA

Sei un fumatore di età compresa fra 21 e 65 anni?
Ti hanno diagnosticato un problema rientrante nei disturbi
dello spettro schizofrenico?
Vuoi provare la sigaretta elettronica?

SCOPO

Ricercatori appartenenti a: Weill Cornell Medicine, Hunter College, University of Stirling, Scozia, King's College, Londra, e Università di Catania, Italia stanno valutando se le sigarette elettroniche possono essere usate come strumento per la disassuefazione dal tabagismo

PROCEDURE

Ai partecipanti sarà fornito un nuovo modello di e-cigarette per provarla come alternativa alla sigaretta classica, e verranno seguiti per 3 mesi. La partecipazione implica la compilazione di questionari e diari, e valutazioni su aspetti fisici e comportamentali.

COMPENSO

I partecipanti non riceveranno alcun compenso per la partecipazione a questo studio

PER PARTICIPARE:

Se siete interessati, o desiderate più informazioni, per favore contattate Pasquale Caponnetto, Ricercatore Unict
p.caponnetto@unict.it, o (095)3781537.

PROTOCOLLO: 1607017418

APPENDIX 9

Health provider information, quantitative study

By signing below, I give the members of the research team permission to contact my medical and or mental health providers, the research team, to confirm eligibility to participate in this study, to inform my providers of my participation in this study, or for any other matter related to this study and my well-being.

Participant ID:

Print Participant Name:

Sign Participant Name:

Date:

Primary Care/Medical Provider

Name:

Phone:

Address:

Mental Health Provider

Name:

Phone:

Address:

Other Health Provider

Name:

Phone:

Address:

APPENDIX 10

Patient information sheet and consent form, quantitative study (Italy and US sites)

| | | |
|--|---|--------------|
| CENTRO PER LA PREVENZIONE E CURA DEL TABAGISMO | MODULO PER L'INFORMAZIONE E IL CONSENSO INFORMATO | |
| Studio :SchizEcig-P | EudraCT N.:(obbligatorio per le sperimentazioni cliniche con medicinali): | Paziente N.: |

Titolo dello studio:

TITOLO: Ruolo della sigaretta elettronica nella cessazione da fumo di sigaretta in fumatori con schizofrenia: Studio pilota prospettico a 3 mesi

Gentile paziente, la presente nota informativa Le viene presentata per darLe tutti gli elementi di conoscenza necessari per la Sua partecipazione allo studio clinico in oggetto.

INTRODUZIONE

Obiettivi.

Lo scopo di questo studio è quello di vedere se fumatori di sigarette di tabacco con diagnosi di disturbo appartenente allo spettro di schizofrenico passano dalla sigaretta classica alla sigaretta elettronica quando sono invitati a provare l'elettronica. Siamo anche interessati a conoscere la vostra esperienza utilizzando la e-cigarette, come si sente quando la fuma, il grado di soddisfazione e la sua accettabilità per sostituire le sigarette classiche e se causa fastidi, come ad esempio la bocca asciutta. Questo studio di ricerca è stato fatto perché le sigarette elettroniche sono oramai ampiamente utilizzate e sappiamo molto poco su fumatori con disturbi appartenenti allo spettro di schizofrenico che utilizzano la e-cigarette.

DESCRIZIONE DELLO STUDIO

Che cosa deve sapere riguardo la “e-cigarette”. La “e-cigarette” è un dispositivo elettronico a batteria che rilascia nicotina e che ricorda da vicino la forma di una sigaretta classica. La batteria al litio ha una capacità di 250 mAh e verrà completamente caricata prima dell'uso. I cartomizzatori saranno riempiti con circa 1 ml di liquido. Questi saranno forniti gratuitamente dal fabbricante.

Come e dove verrà condotto questo studio clinico? Questo studio clinico verrà condotto presso il CENTRO PER LA PREVENZIONE E CURA DEL TABAGISMO, A.O.U “Policlinico-V. Emanuele”, Pad n°4, piano 0, stanza 2, Via S. Sofia 78, 95100 Catania. Venti fumatori riceveranno fornitura gratuita per 12 settimane di cigarette elettroniche modello “cigalike”. Si ricordi che è molto importante che Lei si impegni a presentarsi a tutte le visite presso l'ospedale e che segua le istruzioni fornite. Le affinché lo studio possa andare bene.

Che cosa dovrà fare nel corso di questo studio clinico? Ci saranno un totale di 4 visite presso l'ospedale. Ogni visita richiederà approssimativamente 15 minuti per il completamento. Se Lei acconsente a partecipare allo studio, per prima cosa entrerà in una fase di screening che ha lo scopo di identificare se Lei soddisfa i criteri per la partecipazione allo studio. Nel corso dello studio inoltre, i ricercatori Le chiederanno se ha avuto degli effetti indesiderati. Per la prima visita verranno raccolti i dati socio-demografici, verrà dettagliatamente analizzata la dipendenza da nicotina. La dipendenza dalla sigaretta sarà misurata con il Fagerström Test for Cigarette Dependence (FTCD). Inoltre, i livelli di monossido di carbonio nell'aria espirata (eCo) saranno misurati utilizzando un dispositivo portatile (Micro CO, Micro Medical Ltd, UK). Verranno anche registrati alla baseline i parametri vitali di pressione arteriosa, frequenza cardiaca (HR e BP) e peso corporeo. Verranno inoltre valutati i sintomi positive e negati della Schizofrenia attraverso le scale Scale for the Assessment of Negative symptoms of Schizophrenia (SANS), Scale for the Assessment of Positive symptoms of Schizophrenia (SAPS). Lei sarà inoltre invitato a compilare un diario giornaliero per registrare la sua esperienza con la sigaretta elettronica. Alla settimana 4- (visita di studio 2), settimana-8 (visita di studio 3), settimana-12 (visita di studio 4), i partecipanti mostreranno i diari, b) saranno registrati i loro livelli di eCo, segni vitali, peso, punteggi ai test SAPS, SANS e “Modified Cigarette Evaluation Questionnaire (mCEQ)”. Conservi le sigarette

elettroniche che le sono state date durante le visite dello studio in un posto sicuro, e le tenga al di fuori della portata dei bambini o di altre persone che non possano comprendere il rischio potenziale del fumo. Non deve dare la sigaretta elettronica a nessun altro. Si ricordi inoltre di restituire sia le sigarette elettroniche utilizzate che quelle non utilizzate ai ricercatori dello studio ad ogni visita presso l'ospedale. Si raccomanda di aspirare lentamente e di non compiere più di tre, quattro boccate consecutive, per evitare il surriscaldamento del vaporizzatore e/o la fuoriuscita del liquido. Il dispositivo non è impermeabile. Evitare che si bagni. Non lasciare il dispositivo in ambienti particolarmente caldi o freddi. Temperature troppo elevate o troppo basse possono danneggiare e ridurre la durata dei circuiti elettrici e delle batterie. Il Suo medico dello studio dovrà essere informato riguardo ai farmaci che sta assumendo, incluse tutte le medicine che può comprare liberamente, senza l'obbligo di prescrizione (la ricetta del medico), in modo che possa controllare se va bene che Lei continui ad assumerle mentre partecipa allo studio. È inoltre importante che non assuma altre medicine per il trattamento antifumo mentre partecipa a questo studio. Se darà il Suo consenso, i ricercatori dello studio informeranno il Suo medico di medicina generale (medico di famiglia) che Lei sta partecipando a questo studio clinico. Nel caso in cui Lei cambi indirizzo durante lo studio, informi cortesemente i ricercatori dello studio.

RISCHI ED INCONVENIENTI POTENZIALI

Quali sono i rischi correlati a questo studio clinico? L'uso della sigaretta elettronica può dare degli effetti indesiderati. Gli effetti indesiderati più ricorrenti sono irritazione della bocca e della gola, tosse.

BENEFICI

La sigaretta elettronica può rappresentare un'alternativa a basso rischio rispetto al fumo di sigaretta tradizionale.

PARTECIPAZIONE ALLO STUDIO

La Sua partecipazione allo studio è totalmente volontaria; un Suo eventuale rifiuto non influirà in alcun modo sulla qualità dell'assistenza e dei trattamenti medici ritenuti opportuni per il Suo caso. Se successivamente alla firma di questo consenso informato si rendessero disponibili nuove informazioni sulla sigaretta elettronica, sullo studio a cui sta partecipando o sulla tipologia di dati da raccogliere, Le saranno

tempestivamente comunicate dal medico sperimentatore. Lei sarà comunque libero di ritirare il Suo consenso in qualsiasi momento, senza che ciò comprometta le cure che Lei riceverà in seguito. D'altra parte Lei potrà essere escluso dallo studio in ogni momento, anche contro la Sua volontà, qualora lo sperimentatore lo ritenga necessario per la Sua salute o per la corretta conduzione dello studio. Lo studio è stato approvato dalle Autorità competenti e sarà condotto in accordo alle normative vigenti in materia di ricerca clinica.

Posso ritirarmi da questo studio? Le ricordiamo che la Sua partecipazione a questo studio clinico è volontaria, quindi può ritirare il Suo consenso alla partecipazione in qualsiasi momento, senza dover dare alcuna motivazione. Nel caso in cui Lei decida di ritirarsi in anticipo dallo studio o la Sua partecipazione è interrotta, è importante, per la Sua sicurezza, che effettui un'ultima visita presso l'ospedale.

SPERIMENTAZIONE CHE PREVEDE: Sostitutivo Nicotinico (Sigaretta Elettronica)

Ai sensi e per gli effetti dell'Art 10 della L. 675/96, io sottoscritto/a.....dichiaro di essere stato informato in modo chiaro e comprensibile che per la sperimentazione a cui volontariamente mi sottopongo presso il Centro Universitario per la Prevenzione e Cura del Tabagismo è necessario l'uso per un totale di 3 mesi della sigaretta elettronica.

Di tale sperimentazione mi sono stati spiegati l'obiettivo ed i possibili effetti collaterali. Dichiaro di acconsentire al trattamento proposto

- Sono stato/a informato/a degli effetti collaterali che la l'uso della sigaretta elettronica potrebbe indurre.
- Confermo di aver informato il medico di ogni mia patologia o condizione passata e presente e di ogni trattamento farmacologico e/o psicoterapico effettuato.
- Confermo di voler sottopormi alla sperimentazione di mia spontanea volontà, senza alcuna compulsione fisica o morale.

Nome e Cognome.....Indirizzo.....

Tel.....Firma del paziente.....

Il sottoscritto Dott..... confermo di aver illustrato in dettaglio la natura, lo scopo e i possibili rischi delle tecniche in oggetto al paziente sopra indicato, che ha dato il proprio consenso a sottoporsi al trattamento.

Nome e CognomeFirma

Data...../...../.....

ALL. 1 - G.P. del. 24/07/08

INFORMATIVA E MANIFESTAZIONE DEL CONSENSO AL TRATTAMENTO DEI DATI PERSONALI ¹

Titolari del trattamento e relative finalità

Il Centro per la Prevenzione e Cura del Tabagismo (C.P.C.T.) A.O.U “Policlinico Vittorio Emanuele”, U.O.C. di Medicina Interna e Medicina d’Urgenza, promotore dello studio che Le è stato descritto, in accordo alle responsabilità previste dalle norme della buona pratica clinica (decreto-legge n. 211/2003), tratteranno i Suoi dati personali, in particolare quelli sulla salute e, soltanto nella misura in cui sono indispensabili in relazione all’obiettivo dello studio, altri dati relativi alla Sua origine e ai Suoi stili di vita esclusivamente in funzione della realizzazione dello studio. A tal fine i dati indicati saranno raccolti dal Centro di sperimentazione. Il trattamento dei dati personali relativi alla Sua salute è indispensabile allo svolgimento dello studio: il rifiuto di conferirli non Le consentirà di parteciparvi.

Natura dei dati

Il medico che La seguirà nello studio La identificherà con un codice. I dati che La riguardano raccolti nel corso dello studio, ad eccezione del Suo nominativo, saranno registrati, elaborati e conservati unitamente a tale codice, alla Sua data di nascita, al sesso, al Suo peso, alla Sua statura, alla Sua attività lavorativa e sportiva, alla Sua salute. Soltanto il medico e i soggetti autorizzati potranno collegare questo codice al Suo nominativo.

Modalità del trattamento

I dati, trattati mediante strumenti anche elettronici, saranno diffusi solo in forma rigorosamente anonima, ad esempio attraverso pubblicazioni scientifiche, statistiche e convegni scientifici. La Sua partecipazione allo studio implica che, in conformità alla normativa sulle sperimentazioni cliniche dei medicinali, il personale del Centro Prevenzione e Cura del Tabagismo, il Comitato etico e le autorità sanitarie italiane e straniere potranno conoscere i dati che La riguardano, contenuti anche nella Sua documentazione clinica originale, con modalità tali da garantire la riservatezza della Sua identità.

Esercizio dei diritti

Potrà esercitare i diritti di cui all'art. 7 del Codice (es. accedere ai Suoi dati personali, integrarli, aggiornarli, rettificarli, opporsi al loro trattamento per motivi legittimi, ecc.) rivolgendosi direttamente al centro di sperimentazione (Il Centro per la Prevenzione e Cura del Tabagismo (C.P.C.T.) A.O.U "Policlinico-V. Emanuele", Pad n°4, piano 0, stanza 2, Via S. Sofia 78, 95100 Catania, tel 095.3781537; Fax 095.7435083).

Potrà interrompere in ogni momento e senza fornire alcuna giustificazione la Sua partecipazione allo studio: in tal caso, i campioni biologici a Lei correlati verranno distrutti.

Non saranno inoltre raccolti ulteriori dati che La riguardano, ferma restando l'utilizzazione di quelli eventualmente già raccolti per determinare, senza alterarli, i risultati della ricerca.

Aspetti economici

Lei non dovrà sostenere nessun costo per le visite, prescrizioni mediche, analisi di laboratorio o altre procedure previste dallo studio in quanto a carico dell'azienda promotrice.

Consenso

Sottoscrivendo tale modulo acconsento al trattamento dei miei dati personali per gli scopi della ricerca nei limiti e con le modalità indicate nell'informativa fornitami con il presente documento.

Nome e Cognome dell'interessato (in stampatello)_____

Firma dell'interessato_____

Data_____

ULTERIORI INFORMAZIONI

Per qualunque domanda, richiesta di chiarimento o problema riguardo al presente studio non esiti a contattare il medico qui di seguito indicato:

Dott. _____ Tel. N° 0953781537

Indirizzo Centro per la Prevenzione e Cura del Tabagismo (C.P.C,T.) A.O.U
"Policlinico-V. Emanuele", Pad n°4, piano 0, stanza 2, Via S. Sofia 78, 95100
Catania.

¹ Da sottoporre agli interessati unitamente al modulo di con senso informato che
descrive le caratteristiche scientifiche dello studio, anche mediante integrazione
dello stesso.

versione 2.0 del 06 Maggio 2017

WEILL CORNELL MEDICAL COLLEGE

Informed Consent and HIPAA Authorization for Clinical Investigation

Project Title: Role of an electronic cigarette on smoking displacement in smokers with
schizophrenia: A prospective 3-month pilot study

Research Project #: 1607017418

Principal Investigator: Jason Kim, MD

INSTITUTION: Weill Cornell Medical College and Hunter Bellevue School of Nursing at Hunter College, City University of New York.

INTRODUCTION

You are invited to consider participating in a research study. You were selected as a possible participant in this study because you are a cigarette smoker with a diagnosis of a schizophrenia spectrum disorder.

Please take your time to make your decision. It is important that you read and understand several general principles that apply to all who take part in our studies:

- (a) Taking part in the study is entirely voluntary.
- (b) Personal benefit to you may or may not result from taking part in the study, but knowledge gained from your participation may benefit others.
- (c) You may decide not to participate in the study or you may decide to stop participating in the study at any time without loss of any benefits to which you are entitled.

The purpose and nature of the study, possible benefits, risks, and discomforts, other options, your rights as a participant, and other information about the study are discussed below. Any new information discovered which might affect your decision to participate or remain in the study will be provided to you while you are a participant in this study. You are urged to ask any questions you have about this study with members of the research team. You should take whatever time you need to discuss the study with your

physician and family. The decision to participate or not is yours. If you decide to participate, please sign and date where indicated at the end of this form.

The study will take place at the Weill Cornell Medical College Clinical and Translational Science Center Adult Outpatient Clinic located at 525 East 68th Street, New York, NY 10065. This study is a collaboration between researchers at the Weill Cornell Medical College and Hunter Bellevue School of Nursing (HBSON). Funding to run this study is provided from a CTSC-HBSON grant. The recipient of the grant is Jennifer DiPiazza, PMHNP-BC Assistant Professor at HBSON, who will be a co-investigator in this study.

WHY IS THE STUDY BEING DONE?

The purpose of this study is to see if tobacco cigarette smokers with a schizophrenia spectrum disorder diagnosis switch from tobacco cigarettes to electronic cigarettes (e-cigarettes) when they are invited to try an e-cigarette. We are also interested in their experiences using the e-cigarette, such as how an e-cigarette feels when it is inhaled, the extent of satisfaction and acceptability of e-cigarettes as substitutes for tobacco cigarettes, and if they feel e-cigarette use is causing any discomfort, for example a dry mouth. This research study is being done because e-cigarettes are becoming widely used and we know very little about cigarette smokers with schizophrenia, interested in trying an e-cigarette, and their experiences when using an e-cigarette.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 40 participants will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

If you take part in this study, you will participate in a variety of procedures and assessments. The table below reflects the assessments and procedures that will occur during each visit, as indicated by an 'x.'

| <u>Procedure</u> | <u>Visit</u> <u>1</u> | <u>Visit</u> <u>2</u> | <u>Visit</u> <u>3</u> | <u>Visit</u> <u>4</u> |
|---------------------------------------|--|--|--|--|
| Contact Information form | x | | | |
| Health Care Provider Information Form | x | | | |

| | | | | |
|---|---|---|---|---|
| Demographic and Smoking History Status form (DSH) | x | | | |
| Vital signs and weight | x | x | x | x |
| Exhaled Carbon Monoxide (eCO) | x | x | x | x |
| Fagerström Test for Nicotine Dependence-Revised (FTND-R) | x | | | |
| Scale for the Assessment of Negative symptoms of Schizophrenia (SANS) | x | x | x | x |
| Scale for the Assessment of Positive symptoms of Schizophrenia (SAPS) | x | x | x | x |
| Modified Cigarette Evaluation Questionnaire (mCEQ) | | x | x | x |
| Study diary | | x | x | x |
| Dispense supply of e-cigarettes | x | x | x | |
| Collect unused e-cigarettes | | | | x |

Description of Assessments and Procedures

DSH: The purpose of the DSH is to learn more about you. For example, you will be asked your age and the amount of cigarettes you smoke daily.

Vital signs: The purpose of assessing your vital signs is to establish a baseline from which to refer back to at each study visit. If there is a dramatic change in your vital signs this will alert us to refer you to your medical provider for further assessment.

eCO: The purpose of measuring eCO (expired carbon monoxide) is to assess the level of carbon monoxide in your exhaled breath. Cigarette smoking typically increase the level of CO and stopping or reducing smoking typically decreases levels of CO. To measure eCO you will be asked to breathe one or more times into a tube. A reading of your eCO level will appear on the device.

FTND-R: The purpose of completing the 6 question FTND-R is to estimate your level of nicotine dependence. For example, you will be asked how soon after waking you smoke your first cigarette.

SANS: The SANS is an assessment for symptoms of schizophrenia. The purpose of completing this assessment is to establish a baseline of symptoms from which to refer back to at each study visit. If there are a dramatic change in symptoms this will alert us to refer you to your medical provider for further assessment. For example, during this assessment you will be asked about your interest in social activities, your speech will be observed, and you will be asked about your feeling of well-being.

SAPS: The SAPS is an assessment for symptoms of schizophrenia. The purpose of completing this assessment is to establish a baseline of symptoms from which to refer back to at each study. If there are dramatic changes in symptoms this will alert us to refer you to your medical provider for further assessment. For example, during this assessment you will be asked if you have heard voices or other sounds when no one is around or if you are experiencing thoughts that do not seem to be your own.

mCEQ: The purpose of completing the 12 question mCEQ is to learn about your experience using the e-cigarette. For example, you will be asked if you enjoyed the sensations in your throat and chest, if you enjoyed smoking the e-cigarette, and if smoking the e-cigarette reduced your craving to smoke cigarettes.

Study Diary: The purpose of the diary is to track number of cigarettes you smoke on a daily basis, the number of e-cigarette pods used on a daily basis, and any adverse events you feel may be attributed to e-cigarette use.

Dispense supply of e-cig and instructions on how to use e-cigarette: At each study visit you will be given the amount of e-cigarettes that are equivalent to your current smoking status. You will receive enough e-cigarettes to last until your next study visit. At each study visit the research staff will review the instructions for use of the e-cigarette and answer any questions.

Collect Unused E-Cigarettes: At the last study visit you will be asked to return unused e-cigarettes.

Please advise the researchers of any medications you are taking. In addition, if you are taking any over-the-counter drugs or herbal supplements which you have obtained from the drug store, grocery store, etc., you should advise the researchers.

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the study for 16-18 weeks. You will be required to make four in-person visits in the first 12 weeks, and we will follow up with you via telephone or email 4-6 weeks after your last visit. You will also be contacted by phone or email to remind you of upcoming study visits, if you miss a study visit, or if you decide to withdraw from the study. In the first 12 weeks, you may be emailed an online survey for your study diary every day, if you decide to complete your diary via REDCap. The follow-up is to enquire of any changes in your cigarette use behavior, and e-cigarette use, after the end of the study. You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

If you choose to not participate in the study or to leave the study, your regular care will not be affected nor will your relations with WCMC, NewYork-Presbyterian Hospital, your physicians, or other personnel. In addition, you will not lose any of the benefits to which you are entitled.

Withdrawal by investigator, physician, or sponsor

The investigators, physicians or sponsors may stop the study or take you out of the study at any time should they judge that it is in your best interest to do so, if you experience a study-related injury, if you need additional or different medication, or if you do not comply with the study plan. They may remove you from the study for various other administrative and medical reasons. They can do this without your consent.

WHAT ARE THE RISKS OF THE STUDY?

E-cigarette devices may impose a risk. Since the research is still being established it is difficult to say for sure if and which side-effects you may experience and the overall effect-to your health with e-cigarette use. Side effects may include increased addiction to nicotine, nicotine poisoning, changes in heart rate, heart palpitations, coughing, congestion, phlegm, sputum and throat clearing, enhanced sense of taste or smell, unusual gastrointestinal movements, wild/strange dreams, symptoms of

common cold, acne, mouth ulcers, canker sores, hiccups, heartburn, headaches, nausea, shaking, sleeplessness, dizziness, prickly, tingly or itchy skin, muscle cramps, spasms and/or aches, gas, diarrhea, and lipoid pneumonia (a rare form of pneumonia caused by inhalation of a fatty substance). There may also be side effects, other than listed above that we cannot predict. There are also documented reports to the US Food and Drug Administration (FDA) from consumers about devices malfunctioning causing harm to the user.

E-cigarettes deliver nicotine and other chemicals to the lungs. The maximum exposure of e-cigarettes will be the approximately equivalent to your current tobacco smoking status for 12 weeks. This is important for you to understand since nicotine is an addictive substance and theoretically participation in this study might lead you to “crave” more nicotine.

Research procedures described above may involve risks that cannot be anticipated at this time. If we learn of anything that may affect your decision to participate, we will inform you as soon as possible. You will then have a chance to reconsider your continuing participation in the research.

In considering your risks in this study it is also important to know that in 2016, The FDA finalized a rule extending regulatory authority to all tobacco products, including e-cigarettes. FDA now regulates the manufacture, import, packaging, labeling, advertising, promotion, sale, and distribution of e-cigarettes. However, to date e-cigarettes are not currently approved by the FDA, but they are available for purchase to the general public. This means that e-cigarettes, are not currently subject to the FDA review requirements of the Tobacco Control Act, however e-cigarette manufacturers are now required to meet timelines for adhering to FDA regulations.

ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?

We cannot and do not guarantee that you will receive any benefits from this study. We hope the information learned from this study will benefit other cigarette smokers with a schizophrenia spectrum disorder diagnosis who wish to try an e-cigarette as an alternative to cigarettes smoking.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you may choose not to participate in this study.

Confidentiality

Efforts will be made to protect your medical records and other personal information to the extent allowed by law. However, we cannot guarantee absolute confidentiality. Records of study participants are stored and kept according to legal requirements and may be part of your medical record. You will not be identified personally in any reports or publications resulting from this study. Organizations that may request to inspect and/or copy your research and medical records for quality assurance and data analysis include groups such as:

- Weill Cornell Medical College and NewYork-Presbyterian Hospital
- The Institutional Review Board (IRB)
- The Office of Human Research Protection (OHRP)
- Department of Health and Human Services and National Institutes of Health
- The Food and Drug Administration (FDA) and/or their representatives
- Hunter Bellevue School of Nursing at Hunter College will also be consenting participants for this study
- University of Stirling

By signing this consent form, you authorize access to this confidential information. You also authorize the release of your medical records to Weill Cornell Medical College and NewYork-Presbyterian Hospital by any other hospitals or institutions where you might receive medical care of any kind while you are participating in this study. In case of reported or observed adverse event, you give the principal investigator and members of the study team permission to consult with your medical or mental health provider.

If information about your participation in this study is stored in a computer, we will take the following precautions to protect it from unauthorized disclosure, tampering, or damage by requiring a unique ID and password to log into the database: We will protect your confidentiality by 1) using REDCap a secure data management system to collect all data, 2) assigning a code to your name and contact information and stored in a password protected computer database, 3) identifying your information using the code assigned throughout the study, without revealing your actual identity, 4) giving access to your data (study specific records in the database and your personal information) only to research personnel directly involved in this study.

HIPAA AUTHORIZATION TO USE or DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH

Purposes for Using or Sharing Protected Health Information: If you decide to join this study, WCMC researchers need your permission to use your protected health information. If you give permission, Weill Cornell Medical College (WCMC) and/or NewYork-Presbyterian Hospital (NYPH) researchers may use your information or share (disclose) information about you for their research that is considered to be protected health information.

Voluntary Choice: The choice to give WCMC and/or NYPH researcher's permission to use or share your protected health information for their research is voluntary. It is completely up to you. No one can force you to give permission. However, you must give permission for WCMC and/or NYPH researchers to use or share your protected health information if you want to participate in the study. If you decline to sign this form, you cannot participate in this study, because the researchers will not be able to obtain and/or use the information they need in order to conduct their research. Refusing to give permission will not affect your ability to get usual treatment, or health care from WCMC and/or NYPH.

Protected Health Information To Be Used or Shared: Your personal health information will be used to ensure that you meet the eligibility criteria. If you are not a patient at WCMC your current medical providers will be contacted and asked for your personal health information to ensure that you meet the eligibility criteria. To support safe participation in the study throughout the investigation, the research staff will review a variety of measures as outlined above in the "procedures and assessments" section of this consent form. These measures include Scale for the Assessment of Negative Symptoms of Schizophrenia (SANS), Scale for the Assessment of Positive Symptoms of Schizophrenia (SAPS), and the study diary.

Other Use and Sharing of Protected Health Information:

Your information will not be shared with the company that is supplying the e-cigarette, Pax Labs, Inc.

CANCELING AUTHORIZATION

Canceling Permission: If you give the WCMC and/or NYPH researchers permission to use or share your protected health information, you have the right to cancel your permission whenever you want. However, canceling your permission will not apply to information that the researchers have already used or shared.

If you wish to cancel your permission, you may do so at any time by writing to:

Privacy Officer

1300 York Avenue, Box 303

New York, NY 10065

If you have questions about this, call: (212) 746-1179 or e-mail: privacy@med.cornell.edu

End of Permission: Unless you cancel it, permission for WCMC and/or NYPH researchers to use or share your protected health information for their research will never end.

ACCESS TO RESEARCH RECORDS

During the course of this study, you will have access to see or copy your protected health information as described in this authorization form in accordance with Weill Cornell Medical College (WCMC) and/or New York-Presbyterian Hospital (NYPH) policies. During your participation in this study, you will have access to your research record and any study information that is part of that record.

WHAT ARE THE COSTS?

There will be no costs to you for your participation. The e-cigarette device will be provided free of charge by Pax Labs, Inc.

POLICY/PROCEDURES FOR RESEARCH RELATED INJURY

You will not be compensated for research related injury.

The Policy and Procedure for Weill Cornell Medical College are as follows: We are obligated to inform you about WCMC's policy in the event injury occurs. If, as a result of your participation, you experience injury from known or unknown risks of the research

procedures as described, immediate medical care and treatment, including hospitalization, if necessary, will be available at the usual charge for such treatment. No monetary compensation is available from WCMC or NewYork-Presbyterian Hospital. Further information can be obtained by calling the Institutional Review Board at (646) 962-8200.

COMPENSATION FOR PARTICIPATION

You will not receive compensation for participating in this study. You should not expect anyone to pay you for pain, worry, lost income, or non-medical care costs that occur from taking part in this research study.

COMMERCIAL INTEREST

There are no commercial interests in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose to not take part in the study or to leave the study at any time. If you choose to not participate in the study or to leave the study, your regular care will not be affected nor will your relations with the Weill Cornell Medical College, New York-Presbyterian Hospital, your physicians, or other personnel. In addition, you will not lose any of the benefits to which you are entitled.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study, a research-related injury, any problems, unexpected physical or psychological discomforts, or if you think that something unusual or unexpected is happening, call the investigator, Dr. Jason Kim, directly at (212)821-0712, or the Department of Psychiatry emergency room at Cornell Medical Center, (212)746-0711, or the Adult Emergency Department at (212)746-5050/5026. Please inform the emergency room physician about their participation in the study. If you have questions about your rights as a research participant, contact the WCMC IRB Office. Direct your questions to:

Institutional Review Board at:

Address: 1300 York Avenue

Telephone: (646) 962-8200

Box 89, New York, New York 10065

Consent for Research Study

Project Title: Role of an electronic cigarette on smoking displacement in smokers with schizophrenia: A prospective 3-month pilot study

Principal Investigator: Jason Kim, M.D.

RESEARCHER'S STATEMENT

I have fully explained this study to the participant. As a representative of this study, I have explained the purpose, the procedures, the benefits and risks that are involved in this research study. Any questions that have been raised have been answered to the individual's satisfaction.

Signature of person obtaining the consent

Print Name of Person

Date

(Principal Investigator or Co-investigator)

PARTICIPANT'S STATEMENT

I, the undersigned, have been informed about this study's purpose, procedures, possible benefits and risks, and I have received a copy of this consent. I have been given the opportunity to ask questions before I sign, and I have been told that I can ask other questions at any time. I voluntarily agree to participate in this study. I am free to withdraw from the study at any time without need to justify my decision. This withdrawal will not in any way affect my future treatment or medical management and I will not lose any benefits to which I otherwise am entitled. I agree to cooperate with Jennifer DiPiazza, PhD, PMHNP-BC and the research staff and to inform them immediately if I experience any unexpected or unusual symptoms.

Signature of Participant

Print Name of Participant

Date

APPENDIX 11

Fagerström Test for Cigarette Dependence – Revised (FTCD)

| Items | Scoring criteria |
|--|---|
| 1. How many cigarettes did you smoke? | 0 = less than 10 1 = 11 – 20 2 = 21 – 30 3 = 31 + |
| 2. Do you smoke more in the morning than the rest of the day? | 0 = never 1 = sometimes 2 = most of the time 3 = always |
| 3. How soon after you wake up do you have your first cigarette? | 3 = within 5 minutes 2 = 6 – 30 minutes 1 = 21 – 30 minutes 0 = after 60 minutes |
| 4. Cigarette most hate to give up | 1 = first in the morning 0 = all others |
| 5. Do you find it hard to refrain from smoking in places where it is forbidden, for example, in church, at the library, in the cinema, etc.? | 0 = never 1 = sometimes 2 = most of the time 3 = always |
| 6. Do you smoke if you are so ill that you are in bed most of the day? | 0 = never 1 = sometimes 2 = most of the time 3 = always |

Scoring

Score of 1 – 2. A patient who scores between 1 and 2 on the Fagerstrom Test for Nicotine Dependence is classified as having a low dependence on nicotine.

Score of 3 – 4. A patient who scores between 3 and 4 would be considered to have low to moderate dependence on nicotine.

Score 5 – 7. A patient who scores between 5 and 7 would be considered to have a moderate dependence on nicotine.

Score 8 and over. A patient who scores 8 and over would be considered highly dependent on nicotine.

APPENDIX 12

Scale for the Assessment of Negative Symptoms (SANS)

Nancy C. Andreasen, M.D., Ph.D. Department of Psychiatry College of Medicine, The University of Iowa, Iowa City, Iowa 52242. Copyright by Nancy C. Andreasen, 1984

1) AFFECTIVE FLATTENING OR BLUNTING

Affective flattening or blunting manifests itself as a characteristic impoverishment of emotional expression, reactivity, and feeling. Affective flattening can be evaluated by observation of the subject's behavior and responsiveness during a routine interview. The rating of some items may be affected by drugs, since the Parkinsonian side-effect of phenothiazines may lead to mask-like facies and diminished associated movements. Other aspects of affect, such as responsivity or appropriateness, will not be affected, however.

Unchanging Facial Expression. The subject's face appears wooden, mechanical, frozen. It does not change expression, or changes less than normally expected, as the emotional content of discourse changes. Since phenothiazines may partially mimic this effect, the interviewer should be careful to note whether or not the subject is on medication, but should not try to "correct" the rating accordingly.

Not at all: Subject is normal or labile 0

Questionable decrease 1

Mild: Occasionally the subject's expression is not as full as expected 2

Moderate: Subject's expressions are dulled overall, but not absent 3

Marked: Subject's face has a flat "set" look, but flickers of affect arise occasionally 4

Severe: Subject's face looks "wooden" and changes little, if at all throughout the interview 5

Decreased Spontaneous Movements. The subject sits quietly throughout the interview and shows few or no spontaneous movements. He does not shift position, move his legs, move his hands, etc., or does so less than normally expected.

Not at all: Subject moves normally or is overactive 0

Questionable decrease 1

Mild: Some decrease in spontaneous movements 2

Moderate: Subject moves three or four times during the interview 3

Marked: Subject moves once or twice during the interview 4

Severe: Subject sits immobile throughout the interview 5

Paucity of Expressive Gestures. The subject does not use his body as an aid in expressing his ideas, through such means as hand gestures, sitting forward in his chair when intent on a subject, leaning back when relaxed, etc. This may occur in addition to decreased spontaneous movements.

Not at all: Subject uses expressive gestures normally or excessively

Questionable decrease 1

Mild: Some decrease in expressive gestures 2

Moderate: Subject uses body as an aid in expression at least three or four times 3

Marked: Subject uses body as an aid in expression only once or twice 4

Severe: Subject never uses body as an aid in expression 5

Poor Eye Contact. The subject avoids looking at others or using his eyes as an aid in expression. He appears to be staring into space even when he is talking.

Not at all: Good eye contact and expression 0 SS14

Questionable decrease 1

Mild: Some decrease in eye contact and eye expression 2

Moderate: Subject's eye contact is decreased by at least half of normal 3

Marked: Subject's eye contact is very infrequent 4

Severe: Subject almost never looks at interviewer 5

Affective Non responsiveness. Failure to smile or laugh when prompted may be tested by smiling or joking in a way which would usually elicit a smile from a normal individual. The examiner may also ask, "Have you forgotten how to smile?" while smiling himself.

Not at all 0

Questionable decrease 1

Mild: Slight but definite lack in responsiveness 2

Moderate: Subject occasionally seems to miss the cues to respond 3

Marked: Subject seems to miss the cues to respond most of the time 4

Severe: Subject is essentially unresponsive, even on prompting 5

Lack of Vocal Inflections. While speaking the subject fails to show normal vocal emphasis patterns. Speech has a monotonic quality, and important words are not emphasized through changes in pitch or volume. Subject also may fail to change volume with changes of subject so that he does not drop his voice when discussing private topics nor raise it as he discusses things which are exciting or for which louder speech might be appropriate.

Not at all: Normal vocal Inflections 0

Questionable decrease 1

Mild: slight decrease in vocal inflections 2

Moderate: Interview notices several instances of flattened vocal inflections 3

Marked: Obvious decrease in vocal inflections 4

Sever: Subject's speech is a continuous monotone 5

Global Rating of Affective Flattening. The global rating should focus on overall severity of affective flattening or blunting. Special emphasis should be given to such core features as unresponsiveness, inappropriateness, and an overall decrease in emotional intensity.

No flattening: Normal affect 0

Questionable affective flattening 1

Mild affective flattening 2

Moderate affective flattening 3

Marked affective flattening 4

Severe affective flattening 5**Inappropriate Affect.** Affect expressed is inappropriate or incongruous, not simply flat or blunted. Most typically, this manifestation of affective disturbance takes the form of smiling or assuming a silly facial expression while talking about a serious or sad subject. (Occasionally subjects may smile or laugh when talking about a serious subject which they find uncomfortable or embarrassing. Although their smiling may seem inappropriate, it is due to anxiety and therefore should not be rated as inappropriate affect.) Do not rate affective flattening or blunting as inappropriate. (This item was in the original SANS. However, subsequent analyses have shown that it loads on a disorganized dimension in factor analyses. Consequently, it should not be used as part of the global rating of affective flattening or in the sum of negative symptoms if three dimensions of psychopathology are being examined.)

Not at all: Affect is not inappropriate 0

Questionable 1

Mild: At least one instance of inappropriate smiling or other inappropriate affect 2

Moderate: Subject exhibits two to four instances of inappropriate affect 3

Marked: Subject exhibits five to ten instances of inappropriate affect 4

Severe: Subject's affect is inappropriate most of the time 5

2) ALOGIA

Alogia is a general term coined to refer to the impoverished thinking and cognition that often occur in subjects with schizophrenia (Greek a = no, none; logos = mind, thought). Subjects with alogia have thinking processes that seem empty, turgid, or slow. Since thinking cannot be observed directly, it is inferred from the subject's speech. The two major manifestations of alogia are nonfluent empty speech (poverty of speech) and fluent empty speech (poverty of content of speech). Blocking and increased latency or response may also reflect alogia.

Poverty of Speech. Restriction in the amount of spontaneous speech, so that replies to questions tend to be brief, concrete, and unelaborated. Unprompted additional information is rarely provided. Replies may be monosyllabic, and some questions may be left unanswered altogether. When confronted with this speech pattern, the interviewer may find himself frequently prompting the subject in order to encourage elaboration of replies. To elicit this finding, the examiner must allow the subject adequate time to answer and to elaborate his answer.

No poverty of speech: A substantial and appropriate number of replies to questions include additional information 0 SS19

Questionable poverty of speech 1

Mild: Occasional replies do not include elaborated information even though this is appropriate 2

Moderate: Some replies do not include appropriately elaborated information, and some replies are monosyllabic or very brief--("Yes." "No." "Maybe." "I don't know." "Last week.") 3

Marked: Answers are rarely more than a sentence or a few words in length 4

Severe: Subject says almost nothing and occasionally fails to answer questions 5

Poverty of Content of Speech. Although replies are long enough so that speech is adequate in amount, it conveys little information. Language tends to be vague, often over-abstract or over-concrete, repetitive, and stereotyped. The interviewer may recognize this finding by observing that the subject has spoken at some length but has not given adequate information to answer the question. Alternatively, the subject may provide enough information, but require many words to do so, so that a lengthy reply can be summarized in a sentence or two. Sometimes the interviewer may characterize the speech as "empty philosophizing."

Exclusions: This finding differs from circumstantiality in that the circumstantial subject tends to provide a wealth of detail.

Example: Interviewer: "Why is it, do you think, that people believe in God?"
Subject: "Well, first of all because he uh, he are the person that is their personal savior. He walks with me and talks with me. And uh, the understanding that I have, um, a lot of peoples, they don't really, uh, know they own personal self. Because, uh, they ain't, they all, just don't know they personal self. They don't, know that he uh, seemed like to me, a lot of 'em don't understand that he walks and talks with them."

No poverty of content 0

Questionable 1

Mild: Occasional replies are too vague to be comprehensible or can be markedly condensed 2

Moderate: Frequent replies which are vague or can be markedly condensed to make up at least a quarter of the interview 3

Marked: At least half of the subject's speech is composed of vague or incomprehensible replies 4

Severe: Nearly all the speech is vague, incomprehensible, or can be markedly condensed 5

Blocking. Interruption of a train of speech before a thought or idea has been completed. After a period of silence which may last from a few seconds to minutes, the person indicates that she/he cannot recall what he had been saying or meant to say. Blocking should only be judged to be present if a person voluntarily describes losing his thought or if, upon questioning by the interviewer, the person indicates that that was the reason for pausing.

No blocking 0

Questionable 1

Mild: A single instance noted during a forty-five minute period 2

Moderate: Occurs twice during forty-five minutes 3

Marked: Occurs three or four times during forty-five minutes 4

Severe: Occurs more than four times in forty-five minutes 5

Increased Latency of Response. The subject takes a longer time to reply to questions than is usually considered normal. He may seem "distant" and sometimes the examiner may wonder if he has even heard the question. Prompting usually indicates that the subject is aware of the question, but has been having difficulty in formulating his thoughts in order to make an appropriate reply.

Not at all 0

Questionable 1

Mild: Occasional brief pauses before replying 2

Moderate: Often pauses several seconds before replying 3

Marked: Usually pauses at least ten to fifteen seconds before replying 4

Severe: Long pauses prior to nearly all replies. 5

Global Rating of Alogia. Since the core features of alogia are poverty of speech and poverty of content of speech, the global rating should place particular emphasis on them.

No alogia 0

Questionable 1

Mild: Mild but definite impoverishment in thinking 2

Moderate: Significant evidence for impoverished thinking 3

Marked: Subject's thinking seems impoverished much of the time 4

Severe: Subject's thinking seems impoverished nearly all of the time 5

3) AVOLITION-APATHY

Avolition manifests itself as a characteristic lack of energy, drive, and interest. Subjects are unable to mobilize themselves to initiate or persist in completing many different kinds of tasks. Unlike the diminished energy or interest of depression, the avolitional symptom complex in schizophrenia is usually not accompanied by saddened or depressed affect. The avolitional symptom complex often leads to severe social and economic impairment.

Grooming and Hygiene. The subject displays less attention to grooming and hygiene than normal. Clothing may appear sloppy, outdated, or soiled. The subject may bathe infrequently and not care for hair, nails, or teeth--leading to such manifestations as greasy or uncombed hair, dirty hands, body odor, or unclean teeth and bad breath. Overall, the appearance is dilapidated and disheveled. In extreme cases, the subject may even have poor toilet habits.

How often do you bathe or shower?

Do you change your clothes every day?

How often do you do laundry?

No evidence of poor grooming and hygiene 0 SS24

Questionable 1

Mild: Some slight but definite indication of inattention to appearance, i.e., messy hair or disheveled clothes 2

Moderate: Appearance is somewhat disheveled, i.e., greasy hair, dirty clothes 3

Marked: Subject's attempts to keep up grooming or hygiene are minimal 4

Severe: Subject's clothes, body and environment are dirty and smelly 5

Impersistence at Work or School. The subject has had difficulty in seeking or maintaining employment (or schoolwork) as appropriate for his or her age and sex. If a student, he/she does not do homework and may even fail to attend class. Grades will tend to reflect this. If a college student, there may be a pattern of registering for courses, but having to drop several or all of them before the semester is completed. If of working age, the subject may have found it difficult to work at a job because of inability to persist in completing tasks and apparent irresponsibility. He may go to work irregularly, wander away early, complete them in a disorganized manner. He may simply sit around the house and not seek any employment or seek it only in an infrequent and desultory manner. If a housewife or retired person, the subject may fail to complete chores, such as shopping or cleaning, or complete them in an apparently careless and half-hearted way.

Have you been having any problems at (work, school)?

Do you ever start some project and just never get around to finishing it?

No evidence of impersistence at work or school 0

Questionable 1

Mild: Slight indications of impersistence, i.e., missing a couple days of school or work 2

Moderate: Subject often has poor performance at work or school 3

Marked: Subject has much difficulty maintaining even a below normal level of work or school 4

Severe: Subject consistently fails to maintain a record at work or school 5

Physical Anergia. The subject tends to be physically inert. He may sit in a chair for hours at a time and not initiate any spontaneous activity. If encouraged to become involved in an activity, he may participate only briefly and then wander away or disengage himself and return to sitting alone. He may spend large amounts of time in some relatively mindless and physically inactive task such as watching TV or playing solitaire. His family may report that he spends most of his time at home "doing nothing except sitting around". Either at home or in an inpatient setting he may spend much of his time sitting in his room.

Are there times when you lie or sit around most of the day?

(Does this ever last longer than one day?)

No Evidence of Physical Anergia 0

Questionable 1

Mild Anergia 2

Moderate: Subject lies in bed or sits immobile at least a quarter of normal waking hours 3

Marked: Subject lies in bed or sits immobile at least half of normal waking hours 4

Severe: Subject lies in bed or sits immobile for most of the day 5

Global Rating of Avolition – Apathy. The global rating should reflect the overall severity of the avolition symptoms, given expectational norms for the subject's age and social status or origin. In making the global rating, strong weight may be given to only one or two prominent symptoms if they are particularly striking.

No Avolition 0

Questionable 1

Mild, But Definitely Present 2

Moderate Avolition 3

Marked Avolition 4

Severe Avolition 5

4) ANHEDONIA-ASOCIALITY

This symptom complex encompasses the schizophrenic subject's difficulties in experiencing interest or pleasure. It may express itself as a loss of interest in pleasurable activities, an inability to experience pleasure when participating in activities normally considered pleasurable, or a lack of involvement in social relationships of various kinds.

Recreational Interests and Activities. The subject may have few or no interests, activities, or hobbies. Although this symptom may begin insidiously or slowly, there will usually be some obvious decline from an earlier level of interest and activity. Subjects with relatively milder loss of interest will engage in some activities which are passive or non-demanding, such as watching TV, or will show only occasional or sporadic interest. Subjects with the most extreme loss will appear to have a complete and intractable inability to become involved in or enjoy activities. The rating in this area should take both the quality and quantity of recreational interests into account.

Have you felt interested in the things you usually enjoy?

(Have they been as fun as usual?)

Have you been watching TV or listening to the radio?

No Inability to Enjoy Recreational Interests or Activities 0

Questionable 1

Mild Inability to Enjoy Recreational Activities 2

Moderate: Subject often is not "up" for recreational activities 3

Marked: Subject has little interest in and derives only mild pleasure from recreational activities 4

Severe: Subject has no interest in and derives no pleasure from recreational activities 5

Sexual Interest and Activity. The subject may show a decrement in sexual interest and activity, as judged by what would be normal for the subject's age and marital status. Individuals who are married may manifest disinterest in sex or may engage in intercourse only at the partner's request. In extreme cases, the subject may not engage in any sex at all. Single subjects may go for long periods of time without sexual involvement and make no effort to satisfy this drive. Whether married or single, they may report that they subjectively feel only minimal sex drive or that they take little enjoyment in sexual intercourse or in masturbatory activity even when they engage in it.

Have you noticed any changes in your sex drive?

No Inability to Enjoy Sexual Activities 0

Questionable Decrement in Sexual Interest and Activity 1

Mild Decrement in Sexual Interest and Activity 2

Moderate: Subject occasionally has noticed decreased interests in and/or enjoyment from sexual activities 3

Marked: Subject has little interest in and/or derives little pleasure from sexual activities 4

Severe: Subject has no interest in and/or derives no pleasure from sexual activities 5

Ability to Feel Intimacy and Closeness. The subject may display an inability to form close and intimate relationships of a type appropriate for his age, sex, and family status. In the case of a younger person, this area should be rated in terms of relationships with the opposite sex and with parents and siblings. In the case of an older person who is married, the relationship with spouse and with children should be evaluated, while older unmarried individuals should be judged in terms of relationships with the opposite sex and any family members who live nearby. Subjects may display few or no feelings of affection to available family members. Or they may have arranged their lives so that they are completely isolated from any intimate relationships, living alone and making no effort to initiate contacts with family or members of the opposite sex.

Have you been having any problems with your (family, spouse)?
How would you feel about visiting with your (family, parents, spouse, etc.)?

No Inability to Feel Intimacy and Closeness 0

Questionable Inability 1

Mild, But Definite Inability to Feel Intimacy and Closeness 2

Moderate: Subject appears to enjoy family or significant others but does not appear to "look forward" to visits 3

Marked: Subject appears neutral toward visits from family or significant others. Brightens only mildly 4

Severe: Subject prefers no contact with or is hostile toward family or significant others 5

Relationships with Friends and Peers. Subjects may also be relatively restricted in their relationships with friends and peers of either sex. They may have few or no friends, make little or no effort to develop such relationships, and choose to spend all or most of their time alone.

Have you been spending much time with friends?

Do you enjoy spending time alone, or would you rather have more friends?

No Inability to Form Close Friendships 0

Questionable Inability to Form Friendships 1

Mild, But Definite Inability to Form Friendships 2

Moderate: Subject able to interact, but sees friends/acquaintances only two to three times per month 3

Marked: Subject has difficulty forming and/or keeping friendships. Sees friends/acquaintances only one to two times per month 4

Severe: Subject has no friends and no interest in developing any social ties 5

Global Rating of Anhedonia-Asociality. The global rating should reflect the overall severity of the anhedonia-asociality complex, taking into account the norms appropriate for the subject's age, sex, and family status.

No Evidence of Anhedonia-Asociality 0

Questionable Evidence of Anhedonia-Asociality 1

Mild, But Definite Evidence of Anhedonia-Asociality 2

Moderate Evidence of Anhedonia-Asociality 3

Marked Evidence of Anhedonia-Asociality 4

Severe Evidence of Anhedonia-Asociality 5

5) ATTENTION

Attention is often poor in schizophrenics. The subject may have trouble focusing his attention, or he may only be able to focus sporadically and erratically. He may ignore attempts to converse with him, wander away while in the middle of an activity or task, or appear to be inattentive when engaged in formal testing or interviewing. He may or may not be aware of his difficulty in focusing his attention.

In some factor analyses, attentional impairment loads on the disorganized dimension, when three dimensions of psychopathology emerge. Consequently, analyses that examine three dimensions may choose to place this item in the disorganized dimension rather than the negative dimension.

Social Inattentiveness. While involved in social situations or activities, the subject appears inattentive. He looks away during conversations, does not pick up the topic during a discussion, or appears uninvolved or unengaged. He may abruptly terminate a discussion or a task without any apparent reason. He may seem "spacy" or "out of it". He may seem to have poor concentration when playing games, reading, or watching TV.

No Indication of Inattentiveness 0

Questionable Signs 1

Mild, But Definite Signs of Inattentiveness 2

Moderate: Subject occasionally misses what is happening in the environment 3

Marked: Subject often misses what is happening in the environment; has trouble with reading comprehension 4

Severe: Subject unable to follow conversation, remember what he's read, or follow TV plot 5

Inattentiveness During Mental Status Testing. The subject may perform poorly on simple tests of intellectual functioning in spite of adequate education and intellectual ability. This should be assessed by having the subject spell "world" backwards and by serial 7's (at least a tenth grade education) or serial 3's (at least a sixth grade education) for a series of five subtractions. A perfect score is 10.

Questionable: No errors but subject performs in a halting manner or makes/corrects an error 1

Mild, But Definite (One Error) 2

Moderate (Two Errors) 3

Marked (Three Errors) 4

Severe (More Than Three Errors) 5

Global Rating of Attention. This rating should assess the subject's overall ability to attend or concentrate, and include both clinical appearance and performance on tasks.

No Indications of Inattentiveness 0

Questionable 1

Mild, But Definite Inattentiveness 2

Moderate Inattentiveness 3

Marked Inattentiveness 4

Severe Inattentiveness 5

APPENDIX 13

Scale for the Assessment of Positive Symptoms (SAPS)

Nancy C. Andreasen, M.D., Ph.D. Department of Psychiatry, College of Medicine, The University of Iowa, Iowa City, Iowa 52242. Copyright by Nancy C. Andreasen, 1984 (SAS Variable Name edition: 2000)

INTRODUCTION

This scale is designed to assess positive symptoms, principally those that occur in schizophrenia. It is intended to serve as a complementary instrument to the Scale for the Assessment of Negative Symptoms (SANS). These positive symptoms include hallucinations, delusions, bizarre behavior, and positive formal thought disorder.

As in the case of the SANS, the investigator using this instrument will need to decide on an appropriate "time set". The instrument was developed with the exception that, in general, the time set will cover the past month as in the case of SANS. This scale can also be used in psychopharmacologic research in order to make weekly ratings and chart the subject's response to treatment. Investigators using this instrument, particularly in combination with the SANS, will need to use a standard clinical interview in order to evaluate the subject's symptoms. Since positive formal thought disorder is an important positive symptom, it is recommended that, in doing this interview, the investigator begin talking with the subject on a relatively neutral topic for five to ten minutes in order to observe the subject's manner of speaking and responding. Thereafter, he can begin to ask specific questions about the various positive symptoms. Suggested probes are provided in the interview guide.

In addition to using a clinical interview, the investigator should also draw on other sources of information, such as direct observation, reports from the subject's family, reports from nurses, and reports from the subject himself. In general, the subject can usually be considered a relatively reliable informant concerning delusions and hallucinations if he is able to communicate clearly and will comply with a clinical interview. On the other hand, the interviewer

will usually have to rely on observation and reports from outside sources in order to evaluate bizarre behavior and positive formal thought disorder.

1) HALLUCINATIONS

Hallucinations represent an abnormality in perception. They are false perceptions occurring in the absence of some identifiable external stimulus. They may be experienced in any of the sensory modalities, including hearing, touch, taste, smell, and vision. True hallucinations should be distinguished from illusions (which involve a misperception of an external stimulus), hypnogogic and hypnopompic experiences (which occur when the subject is falling asleep or waking up), or normal thought processes that are exceptionally vivid. If the hallucinations have a religious quality, then they should be judged within the context of what is normal for the subject's social and cultural background. Hallucinations occurring under the immediate influence of alcohol, drugs, or serious physical illness should not be rated as present. The subject should always be requested to describe the hallucination in detail.

Auditory Hallucinations. The subject has reported voices, noises, or sounds. The commonest auditory hallucinations involve hearing voices speaking to the subject or calling him names. The voices may be male or female, familiar or unfamiliar, and critical or complimentary. Typically, subjects suffering from schizophrenia experience the voices as unpleasant and negative. Hallucinations involving sounds rather than voices, such as noises or music, should be considered less characteristic and less severe.

Have you ever heard voices or other sounds when no one is around?

What did they say?

None 0

Questionable 1

Mild: Subject hears noises or single words; they occur only occasionally 2

Moderate: Clear evidence of voices; they have occurred at least weekly 3

Marked: Clear evidence of voices which occur almost every day 4

Severe: Voices occur often every day

Voices Commenting. Voices commenting are a particular type of auditory hallucination which phenomenologists as Kurt Schneider consider to be pathognomonic of schizophrenia, although some recent evidence contradicts this. These hallucinations involve hearing a voice that makes a running commentary on the subject's behavior or thought as it occurs. If this is the only type of auditory hallucination that the subject hears, it should be scored instead of auditory hallucinations (No. 1 above). Usually, however, voices commenting will occur in addition to other types of auditory hallucinations.

*Have you ever heard voices commenting on what you are thinking or doing?
What do they say?*

None 0

Questionable 1

Mild: Subject hears noises or single words; they occur only occasionally 2

Moderate: Clear evidence of voices; they have occurred at least weekly 3

Marked: Clear evidence of voices which occur almost every day 4

Severe: Voices occur often every day 5

Voices Conversing. Like voices commenting, voices conversing are considered a Schneiderian first-rank symptom. They involve hearing two or more voices talking with one another, usually discussing something about the subject. As in the case of voices commenting, they should be scored independently of other auditory hallucinations.

*Have you heard two or more voices talking with each other?
What did they say?*

None 0

Questionable 1

Mild: Subject hears noises or single words; they occur only occasionally 2

Moderate: Clear evidence of voices; they have occurred at least weekly 3

Marked: Clear evidence of voices which occur almost every day 4

Severe: Voices occur often every day 5

Somatic or Tactile Hallucinations. These hallucinations involve experiencing peculiar physical sensations in the body. They include burning sensations, tingling, and perceptions that the body has changed in shape or size.

Have you ever had burning sensations or other strange feelings in your body?

What were they?

Did your body ever appear to change in shape or size?

None 0

Questionable 1

Mild: Subject experiences peculiar physical sensations; they occur only occasionally 2

Moderate: Clear evidence of somatic or tactile hallucinations; they have occurred at least weekly 3

Marked: Clear evidence of somatic or tactile hallucinations which occur almost every day 4

Severe: Hallucinations occur often every day 5

Olfactory Hallucinations. The subject experiences unusual smells which are typically quite unpleasant. Sometimes the subject may believe that he himself smells. This belief should be scored here if the subject can actually smell the odor himself, but should be scored among delusions if he only believes that others can smell the odor.

Have you ever experienced any unusual smells or smells that others do not notice?

What were they?

None 0

Questionable 1

Mild: Subject experiences unusual smells; they occur only occasionally 2

Moderate: Clear evidence of olfactory hallucinations; they have occurred at least weekly 3

Marked: Clear evidence of olfactory hallucinations; they occur almost every day 4

Severe: Olfactory hallucinations occur often every day 5

Visual Hallucinations. The subject sees shapes or people that are not actually present. Sometimes these are shapes or colors, but most typically they are figures of people or human-like objects. They may also be characters of a religious nature, such as the Devil or Christ. As always, visual hallucinations involving religious themes should be judged within the context of the subject's cultural background. Hypnagogic and hypnopompic visual hallucinations (which are relatively common) should be excluded, as should visual hallucinations occurring when the subject has been taking hallucinogenic drugs.

Have you had visions or seen things that other people cannot?

What did you see?

Did this occur when you were falling asleep or waking up?

None 0

Questionable 1

Mild: Subject experiences visual hallucinations; they occur only occasionally 2

Moderate: Clear evidence of visual hallucinations; they have occurred at least weekly 3

Marked: Clear evidence of visual hallucinations which occur almost every day 4

Severe: Hallucinations occur often every day 5

Global Rating of Severity of Hallucinations. This global rating should be based on the duration and severity of hallucinations, the extent of the subject's preoccupation with the hallucinations, his degree of conviction, and their effect on his actions. Also consider the extent to which the hallucinations

might be considered bizarre or unusual. Hallucinations not mentioned above, such as those involving taste, should be included in this rating.

None 0

Questionable 1

Mild: Hallucinations definitely present, but occur infrequently; at times the subject may question their existence **2**

Moderate: Hallucinations are vivid and occur occasionally; they may bother him to some extent **3**

Marked: Hallucinations are quite vivid, occur frequently, and pervade his life **4**

Severe: Hallucinations occur almost daily and are sometimes unusual or bizarre; they are very vivid and extremely troubling

2) DELUSIONS

Delusions represent an abnormality in content of thought. They are false beliefs that cannot be explained on the basis of the subject's cultural background. Although delusions are sometimes defined as "fixed false beliefs," in their mildest form delusions may persist only for weeks to months, and the subject may question his beliefs or doubt them. The subject's behavior may or may not be influenced by his delusions. The rating of severity of individual delusions and of the global severity of delusional thinking should take into account their persistence, their complexity, the extent to which the subject acts on them, the extent to which the subject doubts them, and the extent to which the beliefs deviate from those that normal people might have. For each positive rating, specific examples should be noted in the margin.

Persecutory Delusions. People suffering from persecutory delusions believe that they are being conspired against or persecuted in some way. Common manifestations include the belief that one is being followed, that one's mail is being opened, that one's room or office is bugged, that the telephone is tapped, or that police, government officials, neighbors, or fellow workers are harassing the subject. Persecutory delusions are sometimes

relatively isolated or fragmented, but sometimes the subject has a complex set of delusions involving both a wide range of forms of persecution and a belief that there is a well-designed conspiracy behind them. For example, a subject may believe that his house is bugged and that he is being followed because the government wrongly considers him a secret agent for a foreign government; this delusion may be so complex that it explains almost everything that happens to him. The ratings of severity should be based on duration and complexity.

Have people been bothering you in any way?

Have you felt that people are against you?

Has anyone been trying to harm you in any way?

Has anyone been watching or monitoring you?

None 0

Questionable 1

Mild: Delusional beliefs are simple and may be of several different types; subject may question them occasionally 2

Moderate: Clear, consistent delusion that is firmly held 3

Marked: Consistent, firmly-held delusion that the subject acts on 4

Severe: Complex well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre 5

Delusions of Jealousy. The subject believes that his/her mate is having an affair with someone. Miscellaneous bits of information are construed as "evidence". The person usually goes to great effort to prove the existence of the affair, searching for hair in the bedclothes, the odor of shaving lotion or smoke on clothing, or receipts or checks indicating a gift has been bought for the lover. Elaborate plans are often made in order to trap the two together.

Have you ever worried that your husband (wife) might be unfaithful to you?

What evidence do you have?

None 0

Questionable 1

Mild: Delusion clearly present, but the subject may question it occasionally 2

Moderate: Clear consistent delusion that is firmly held 3

Marked: Consistent, firmly-held delusion that the subject acts on 4

Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre

Delusions of Sin or Guilt. The subject believes that he has committed some terrible sin or done something unforgivable. Sometimes the subject is excessively or inappropriately preoccupied with things he did wrong as a child, such as masturbating. Sometimes the subject feels responsible for causing some disastrous event, such as a fire or accident, with which he in fact has no connection. Sometimes these delusions may have a religious flavor, involving the belief that the sin is unpardonable and that the subject will suffer eternal punishment from God. Sometimes the subject simply believes that he deserves punishment by society. The subject may spend a good deal of time confessing these sins to whomever will listen. Have you ever felt that you have done some terrible thing that you deserve to be punished for?

None 0

Questionable 1

Mild: Delusional beliefs may be simple and may be of several different types; subject may question them occasionally 2

Moderate: Clear, consistent delusion that is firmly held 3

Marked: Consistent, firmly-held delusion that the subject acts on 4

Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre

Grandiose Delusions. The subject believes that he has special powers or abilities. He may think he is actually some famous personage, such as a rock star, Napoleon, or Christ. He may believe he is writing some definitive book,

composing a great piece of music, or developing some wonderful new invention. The subject is often suspicious that someone is trying to steal his ideas, and he may become quite irritable if his ideas are doubted.

Do you have any special or unusual abilities or talents?

Do you feel you are going to achieve great things?

None 0

Questionable 1

Mild: Delusional beliefs may be simple and may be of several different types; subject may question them occasionally 2

Moderate: Clear, consistent delusion that is firmly held 3

Marked: Consistent, firmly-held delusion that the subject acts on 4

Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre 5

Religious Delusions. The subject is preoccupied with false beliefs of a religious nature. Sometimes these exist within the context of a conventional religious system, such as beliefs about the Second Coming, the Antichrist, or possession by the Devil. At other times, they may involve an entirely new religious system or a pastiche of beliefs from a variety of religions, particularly Eastern religions, such as ideas about reincarnation or Nirvana. Religious delusions may be combined with grandiose delusions (if the subject considers himself a religious leader), delusions of guilt, or delusions of being controlled. Religious delusions must be outside the range considered normal for the subject's cultural and religious background.

Are you a religious person?

Have you had any unusual religious experiences?

What was your religious training as a child?

None 0

Questionable 1

Mild: Delusional beliefs may be simple and may be of several different types; subject may question them occasionally 2

Moderate: Clear, consistent delusion that is firmly held 3

Marked: Consistent, firmly-held delusion that the subject acts on 4

Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre 5

Somatic Delusions. The subject believes that somehow his body is diseased, abnormal, or changed. For example, he may believe that his stomach or brain is rotting, that his hands or penis have become enlarged, or that his facial features are unusual (dysmorphophobia). Sometimes somatic delusions are accompanied by tactile or other hallucinations, and when this occurs, both should be rated. (For example, the subject believes that he has ball bearings rolling around in his head, placed there by a dentist who filled his teeth, and can actually hear them clanking against one another.)

Is there anything wrong with your body?

Have you noticed any change in your appearance?

None 0

Questionable 1

Mild: Delusional beliefs may be simple and may be of several different types; subject may question them occasionally 2

Moderate: Clear, consistent delusion that is firmly held 3

Marked: Consistent, firmly-held delusion that the subject acts on 4

Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre 5

Ideas and Delusions of Reference. The subject believes that insignificant remarks, statements, or events refer to him or have some special meaning for him. For example, the subject walks into a room, sees people laughing, and suspects that they were just talking about him and laughing at him. Sometimes items read in the paper, heard on the radio, or seen on television are considered to be special messages to the subject. In the case of ideas of reference, the subject is suspicious, but recognizes his idea is

erroneous. When the subject actually believes that the statements or events refer to him, then this is considered a delusion of reference.

Have you ever walked into a room and thought people were talking about you or laughing at you?

Have you seen things in magazines or on TV that seem to refer to you or contain a special message for you?

Have people communicated with you in any unusual ways?

None 0

Questionable 1

Mild: Occasional ideas of reference 2

Moderate: Have occurred at least weekly 3

Marked: Occurs at least two to four times weekly 4

Severe: Occurs frequently 5

Delusions of Being Controlled. The subject has a subjective experience that his feelings or actions are controlled by some outside force. The central requirement for this type of delusion is an actual strong subjective experience of being controlled. It does not include simple beliefs or ideas, such as that the subject is acting as an agent of God or that friends or parents are trying to coerce him to do something. Rather, the subject must describe, for example, that his body has been occupied by some alien force that is making it move in peculiar ways, or that messages are being sent to his brain by radio waves and causing him to experience particular feelings that he recognizes are not his own.

Have you ever felt you were being controlled by some outside force?

None 0

Questionable 1

Mild: Subject has experienced being controlled, but doubts it occasionally 2

Moderate: Clear experience of control, which has occurred on two or three occasions in a week 3

Marked: Clear experience of control, which occurs frequently; behavior may be affected 4

Severe: Clear experience of control which occurs frequently, pervades the subject's life, and often affects his behavior 5

Delusions of Mind Reading. The subject believes that people can read his mind or know his thoughts. This is different than thought broadcasting (see below) in that it is a belief without a percept. That is, the subject subjectively experiences and recognizes that others know his thoughts, but he does not think that they can be heard out loud.

Have you ever had the feeling that people could read your mind?

None 0

Questionable 1

Mild: Subject has experienced mind reading, but doubts it occasionally 2

Moderate: Clear experience of mind reading which has occurred on two or three occasions in a week 3

Marked: Clear experience of mind reading which occurs frequently; behavior may be affected 4

Severe: Clear experience of mind reading which occurs frequently, pervades the subject's life, and often affects his behavior 5

Thought Broadcasting. The subject believes that his thoughts are broadcast so that he or others can hear them. Sometimes the subject experiences his thoughts as a voice outside his head; this is an auditory hallucination as well as a delusion. Sometimes the subject feels his thoughts are being broadcast although he cannot hear them himself. Sometimes he believes that his thoughts are picked up by a microphone and broadcast on the radio or television.

Have you ever heard your own thoughts out loud, as if they were a voice outside your head?

Have you ever felt your thoughts were broadcast so other people could hear them?

None 0

Questionable 1

Mild: Subject has experienced thought broadcasting, but doubts it occasionally 2

Moderate: Clear experience of thought broadcasting which has occurred on two or three occasions in a week 3

Marked: Clear experience of thought broadcasting which occurs frequently; behavior may be affected 4

Severe: Clear experience of thought broadcasting which occurs frequently, pervades the subject's life, and often affects his behavior 5

Thought Insertion. The subject believes that thoughts that are not his own have been inserted into his mind. For example, the subject may believe that a neighbor is practicing voodoo and planting alien sexual thoughts in his mind. This symptom should not be confused with experiencing unpleasant thoughts that the subject recognizes as his own, such as delusions of persecution or guilt.

Have you ever felt that thoughts were being put into your head by some outside force?

Have you ever experienced thoughts that didn't seem to be your own?

None 0

Questionable 1

Mild: Subject has experienced thought insertion, but doubts it occasionally 2

Moderate: Clear experience of thought insertion which has occurred on two or three occasions in a week 3

Marked: Clear experience of thought insertion which occurs frequently; behavior may be affected 4

Severe: Thought insertion which occurs frequently, pervades the subject's life and affects behavior 5

Thought Withdrawal. The subject believes that thoughts have been taken away from his mind. He is able to describe a subjective experience of beginning a thought and then suddenly having it removed by some outside

force. This symptom does not include the mere subjective recognition of alogia.

Have you ever felt your thoughts were taken away by some outside force?

None 0

Questionable 1

**Mild: Subject has experienced thought withdrawal, but doubts it occasionally
2**

**Moderate: Clear experience of thought withdrawal which has occurred on two
or three occasions in a week 3**

**Marked: Clear experience of thought withdrawal which occurs frequently;
behavior may be affected 4**

**Severe: Clear experience of thought withdrawal which occurs frequently,
pervades the subject's life and often affects his behavior 5**

Global Rating of Severity of Delusions. The global rating should be based on duration and persistence of delusions, the extent of the subject's preoccupation with the delusions, his degree of conviction, and their effect on his actions. Also consider the extent to which the delusions might be considered bizarre or unusual. Delusions not mentioned above should be included in this rating.

None 0

Questionable 1

**Mild: Delusion definitely present but, at times, the subject questions the belief
2**

**Moderate: The subject is convinced of the belief, but it may occur infrequently
and have little effect on his behavior 3**

**Marked: The delusion is firmly held; it occurs frequently and affects the
subject's behavior 4**

**Severe: Delusions are complex, well-formed, and pervasive; they are firmly
held and have a major effect on the subject's behavior; they may be somewhat
bizarre or unusual 5**

3) BIZARRE BEHAVIOR

The subject's behavior is unusual, bizarre, or fantastic. For example, the subject may urinate in a sugar bowl, paint the two halves of his body different colors, or kill a litter of pigs by smashing their heads against a wall. The information for this item will sometimes come from the subject, sometimes from other sources, and sometimes from direct observation. Bizarre behavior due to the immediate effects of alcohol or drugs should be excluded. As always, social and cultural norms must be considered in making the ratings, and detailed examples should be elicited and noted.

Clothing and Appearance. The subject dresses in an unusual manner or does other strange things to alter his appearance. For example, he may shave off all his hair or paint parts of his body different colors. His clothing may be quite unusual; for example, he may choose to wear some outfit that appears generally inappropriate and unacceptable, such as a baseball cap backwards with rubber galoshes and long underwear covered by denim overalls. He may dress in a fantastic costume representing some historical personage or a man from outer space. He may wear clothing completely inappropriate to the climatic conditions, such as heavy wools in the midst of summer.

Has anyone made comments about your appearance?

None 0

Questionable 1

Mild: Occasional oddities of dress or appearance 2

Moderate: Appearance or apparel are clearly unusual and would attract attention 3

Marked: Appearance or apparel are markedly odd 4

Severe: Subject's appearance or apparel are very fantastic or bizarre 5

Social and Sexual Behavior. The subject may do things that are considered inappropriate according to usual social norms. For example, he may masturbate in public, urinate or defecate in inappropriate receptacles, or exhibit his sex organs inappropriately. He may walk along the street muttering

to himself, or he may begin talking to people whom he has never met about his personal life (as when riding on a subway or standing in some public place). He may drop to his knees praying and shouting in the midst of a crowd of people, or he may suddenly sit in a yoga position while in the midst of a crowd. He may make inappropriate sexual overtures or remarks to strangers. *Have you ever done anything that others might think unusual or that has called attention to yourself?*

None 0

Questionable 1

Mild: Occasional instances of somewhat peculiar behavior 2

Moderate: Frequent instances of odd behavior 3

Marked: Very odd behavior 4

Severe: Extremely odd behavior which may have a fantastic quality 5

Aggressive and Agitated Behavior. The subject may behave in an aggressive, agitated manner, often quite unpredictably. He may start arguments inappropriately with friends or members of his family, or he may accost strangers on the street and begin haranguing them angrily. He may write letters of a threatening or angry nature to government officials or others with whom he has some quarrel. Occasionally, subjects may perform violent acts such as injuring or tormenting animals, or attempting to injure or kill human beings.

Have you ever done anything to try to harm animals or people?

Have you felt angry with anyone?

How did you express your anger?

None 0

Questionable 1

Mild: Occasional instances 2

Moderate: For example, writing angry letters to strangers 3

Marked: For example, threatening people, public harangues 4

Severe: For example, mutilating animals, attacking people 5

Repetitive or Stereotyped Behavior. The subject may develop a set of repetitive actions or rituals that he must perform over and over. Frequently, he will attribute some symbolic significance to these actions and believe that they are either influencing others or preventing himself from being influenced. For example, he may eat jelly beans every night for dessert, assuming that different consequences will occur depending on the color of the jelly beans. He may have to eat foods in a particular order, wear particular clothes, or put them on in a certain order. He may have to write messages to himself or to others over and over; sometimes this will be in an unusual or occult language.

Are there any things that you feel you have to do?

None 0

Questionable 1

Mild: Occasional instances of ritualistic or stereotyped behavior 2

Moderate: For example, eating or dressing rituals lacking symbolic significance 3

Marked: For example, eating or dressing rituals with a symbolic significance 4

Severe: For example, keeping a diary in an incomprehensible language 5

Global Rating of Severity of Bizarre Behavior. In making this rating, the interviewer should consider the type of behavior, the extent to which it deviates from social norms, the subject's awareness of the degree to which the behavior is deviant, and the extent to which it is obviously bizarre.

None 0

Questionable 1

Mild: Occasional instances of unusual or apparently idiosyncratic behavior; subject usually has some insight 2

Moderate: Behavior which is clearly deviant from social norms and seems somewhat bizarre; subject may have some insight 3

Marked: Behavior which is markedly deviant from social norms and clearly bizarre; subject may have some insight 4

Severe: Behavior which is extremely bizarre or fantastic; may include a single extreme act, e.g., attempting murder; subject usually lacks insight. 5

4) POSITIVE FORMAL THOUGHT DISORDER

Positive formal thought disorder is fluent speech that tends to communicate poorly for a variety of reasons.

The subject tends to skip from topic to topic without warning, to be distracted by events in the nearby environment, to join words together because they are semantically or phonologically alike even though they make no sense, or to ignore the question asked and ask another. This type of speech may be rapid, and it frequently seems quite disjointed. It has sometimes been referred to as "loose associations." Unlike alogia (negative formal thought disorder), a wealth of detail is provided, and the flow of speech tends to have an energetic, rather than an apathetic, quality to it.

In order to evaluate thought disorder, the subject should be permitted to talk at length on some topic, particularly a topic unrelated to his psychopathology, for as long as five to ten minutes. The interviewer should observe closely the extent to which his sequencing of ideas is well connected. In addition, the interviewer should insist that he clarify or elaborate further if the ideas seem vague or incomprehensible. He should also pay close attention to how well the subject can reply to a variety of different types of questions, ranging from simple (Where were you born?) to more complicated (How do you think the present government is doing?)

The anchor points for these ratings assume that the subject has been interviewed for a total of approximately forty-five minutes. If the interview is shorter, the ratings should be adjusted accordingly.

Derailment (Loose Associations). A pattern of spontaneous speech in which the ideas slip off one track onto another which is clearly but obliquely related, or onto one which is completely unrelated. Things may be said in juxtaposition which lack a meaningful relationship, or the subject may shift idiosyncratically from one frame of reference to another. At times there may

be a vague connection between the ideas, and at others none will be apparent. This pattern of speech is often characterized as sounding "disjointed." Perhaps the commonest manifestation of this disorder is a slow, steady slippage, with no single derailment being particularly severe, so that the speaker gets farther and farther off the track with each derailment without showing any awareness that his reply no longer has any connection with the question which was asked.

This abnormality is often characterized by lack of cohesion between clauses and sentences and by unclear pronoun references.

Example: Interviewer: "Did you enjoy college?" Subject: "Um-hum. Oh hey well, I oh, I really enjoyed some communities I tried it, and the, and the next day when I'd be going out, you know, um, I took control like uh, I put, um, bleach on my hair in, in California. My roommate was from Chicago, and she was going to the junior college. And we lived in the Y.M.C.A., so she wanted to put it, um, peroxide on my hair, and she did, and I got up and looked at the mirror and tears came to my eyes. Now do you understand it, I was fully aware of what was going on but why couldn't I, I . . . why, why the tears? I can't understand that, can you?"

None 0

Questionable 1

Mild: Occasional instances of derailment, with only slight topic shifts 2

Moderate: Several instances of derailment; subject is sometimes difficult to follow 3

Marked: Frequent instances of derailment; subject is often difficult to follow 4

Severe: Derailment so frequent and/or extreme that the subject's speech is almost incomprehensible 5

Tangentiality. Replying to a question in an oblique, tangential or even irrelevant manner. The reply may be related to the question in some distant way. Or the reply may be unrelated and seem totally irrelevant. In the past tangentiality has sometimes been used as roughly equivalent to loose associations or derailment. The concept of tangentiality has been partially

redefined so that it refers only to answers to questions and not to transitions in spontaneous speech.

Example: Interviewer: "What city are you from?" Subject: "That's a hard question to answer because my parents . . . I was born in Iowa, but I know that I'm white instead of black, so apparently I came from the North somewhere and I don't know where, you know, I really don't know whether I'm Irish or Scandinavian or I don't, I don't believe I'm Polish but I think I'm, I think I might be German or Welsh.

None 0

Questionable 1

Mild: One or two oblique replies 2

Moderate: Occasional oblique replies (three to four times) 3

Marked: Frequent oblique replies (more than four times) 4

Severe: Tangentiality so severe that interviewing the subject is extremely difficult 5

Incoherence (Word Salad, Schizophasia). A pattern of speech which is essentially incomprehensible at times. Incoherence is often accompanied by derailment. It differs from derailment in that in incoherence the abnormality occurs within the level of the sentence or clause, which contains words or phrases that are joined incoherently.

The abnormality in derailment involves unclear or confusing connections between larger units, such as sentences or clauses.

This type of language disorder is relatively rare. When it occurs, it tends to be severe or extreme, and mild forms are quite uncommon. It may sound quite similar to Wernicke's aphasia or jargon aphasia, and in these cases the disorder should only be called incoherence when history and laboratory data exclude the possibility of a past stroke, and formal testing for aphasia is negative.

Exclusions: Mildly ungrammatical constructions or idiomatic usages characteristic of particular regional or ethnic backgrounds, lack of education, or low intelligence.

Example: Interviewer: "What do you think about current political issues like the energy crisis?" Subject: "They're destroying too many cattle and oil just to make soap. If we need soap when you can jump into a pool of water, and then when you go to buy your gasoline, my folks always thought they should, get pop but the best thing to get, is motor oil, and, money. May, may as well go there and, trade in some, pop caps and, uh, tires, and tractors to group, car garages, so they can pull cars away from wrecks, is what I believed in."

None 0

Questionable 1

Mild: Occasional instances of incoherence 2

Moderate: Frequent bursts of incoherence 3

Marked: At least half of the subject's speech is incomprehensible 4

Severe: Almost all of the subject's speech is incomprehensible 5

Illogicality. A pattern of speech in which conclusions are reached which do not follow logically. This may take the form of non-sequiturs (= it does not follow), in which the subject makes a logical inference between two clauses which is unwarranted or illogical.

It may take the form of faulty inductive inferences. It may also take the form of reaching conclusions based on faulty premises without any actual delusional thinking.

Exclusions: Illogicality may either lead to or result from delusional beliefs. When illogical thinking occurs within the context of a delusional system, it should be subsumed under the concept of delusions and not considered a separate phenomenon representing a different type of thinking disorder. Illogical thinking which is clearly due to cultural or religious values or to intellectual deficit should also be excluded.

Example: "Parents are the people that raise you. Anything that raises you can be a parent. Parents can be anything -- material, vegetable, or mineral -- that has taught you something. Parents would be the world of things that are alive, that are there. Rocks -- a person can look at a rock and learn something from it, so that would be a parent."

None 0

Questionable 1

Mild: Occasional instances of illogicality 2

Moderate: Frequent instances of illogicality (three or four times) 3

Marked: Much of the subject's speech is illogical (more than four times) 4

Severe: Most of the subject's speech is illogical 5

Circumstantiality. A pattern of speech which is very indirect and delayed in reaching its goal idea. In the process of explaining something, the speaker brings in many tedious details and sometimes makes parenthetical remarks. Circumstantial replies or statements may last for many minutes if the speaker is not interrupted and urged to get to the point. Interviewers will often recognize circumstantiality on the basis of needing to interrupt the speaker in order to complete the process of history-taking within an allotted time. When not called circumstantial, these people are often referred to as "long-winded."

Exclusions: Although it may coexist with instances of poverty of content of speech or loss of goal, it differs from poverty of content of speech in containing excessive amplifying or illustrative detail and from loss of goal in that the goal is eventually reached if the person is allowed to talk long enough. It differs from derailment in that the details presented are closely related to some particular goal or idea and that the particular goal or idea must be, by definition, eventually reached.

None 0

Questionable 1

Mild: Occasional instances of circumstantiality 2

Moderate: Frequent instances of circumstantiality 3

Marked: At least half of subject's speech is circumstantial 4

Severe: Most of the subject's speech is circumstantial 5

Pressure of Speech. An increase in the amount of spontaneous speech as compared to what is considered ordinary or socially customary. The subject talks rapidly and is difficult to interrupt. Some sentences may be left uncompleted because of eagerness to get on to a new idea. Simple questions

which could be answered in only a few words or sentences are answered at great length so that the answer takes minutes rather than seconds and indeed may not stop at all if the speaker is not interrupted.

Even when interrupted, the speaker often continues to talk. Speech tends to be loud and emphatic. Sometimes speakers with severe pressure will talk without any social stimulation and talk even though no one is listening. When subjects are receiving phenothiazines or lithium, their speech is often slowed down by medication, and then it can be judged only on the basis of amount, volume, and social appropriateness. If a quantitative measure is applied to the rate of speech, then a rate greater than 150 words per minute is usually considered rapid or pressured. This disorder may be accompanied by derailment, tangentiality, or incoherence, but it is distinct from them.

None 0

Questionable 1

Mild: Slight pressure of speech; some slight increase in amount, speed, or loudness of speech 2

Moderate: Usually takes several minutes to answer simple questions, may talk when no one is listening, and/or speaks loudly and rapidly 3

Marked: Frequently talks as much as three minutes to answer simple questions; sometimes begins talking without social stimulation; difficult to interrupt 4

Severe: Subject talks almost continually, cannot be interrupted at all, and/or may shout to drown out the speech of others 5

Distractible Speech. During the course of a discussion or interview, the subject stops talking in the middle of a sentence or idea and changes the subject in response to a nearby stimulus, such as an object on a desk, the interviewer's clothing or appearance, etc.

Example: "Then I left San Francisco and moved to . . . where did you get that tie? It looks like it's left over from the 50's. I like the warm weather in San Diego. Is that a conch shell on your desk? Have you ever gone scuba diving?"

None 0

Questionable 1

Mild: Is distracted once during an interview 2

Moderate: Is distracted from two to four times during an interview 3

Marked: Is distracted from five to ten times during an interview 4

Severe: Is distracted more than ten times during an interview 5

Clanging. A pattern of speech in which sounds rather than meaningful relationships appear to govern word choice, so that the intelligibility of the speech is impaired and redundant words are introduced. In addition to rhyming relationships, this pattern of speech may also include punning associations, so that a word similar in sound brings in a new thought.

Example: I'm not trying to make a noise. I'm trying to make sense. If you can make sense out of nonsense, well, have fun. I'm trying to make sense out of sense. I'm not making sense (cents) anymore. I have to make dollars."

None 0

Questionable 1

Mild: Occurs once during an interview 2

Moderate: Occurs from two to four times during an interview 3

Marked: Occurs five to ten times during an interview 4

Severe: Occurs more than ten times, or so frequently that the interview is incomprehensible.

Global Rating of Positive Formal Thought Disorder. In making this rating, the interviewer should consider the type of abnormality, the degree to which it affects the subject's ability to communicate, the frequency with which abnormal speech occurs, and its degree of severity.

None 0

Questionable 1

Mild: Occasional instances of disorder; subject's speech is understandable 2

Moderate: Frequent instances of disorder; subject is sometimes hard to understand 3

Marked: Subject is often difficult to understand 4

Severe: Subject is incomprehensible 5

APPENDIX 14

Modified Cigarette Evaluation Questionnaire (mCEQ) adapted for e-cigarette users

Instructions: Please read each item below and mark the number that best represents how using your e-cigarette or vaping made you feel.

1- not at all, 2-very little, 3-a little, 4-moderately, 5-a lot, 6-quite a lot, 7 extremely

1. Was using your e-cigarette satisfying? 1 2 3 4 5 6 7
2. Did the e-cigarette taste good? 1 2 3 4 5 6 7
3. Did you enjoy the sensations in your throat and chest? 1 2 3 4 5 6 7
4. Did using your e-cigarette calm you down? 1 2 3 4 5 6 7
5. Did using your e-cigarette make you feel more awake? 1 2 3 4 5 6 7
6. Did using your e-cigarette make you feel less irritable? 1 2 3 4 5 6 7
7. Did using your e-cigarette help you to concentrate? 1 2 3 4 5 6 7
8. Did using your e-cigarette reduce your hunger for food? 1 2 3 4 5 6 7
9. Did using your e-cigarette make you dizzy? 1 2 3 4 5 6 7
10. Did using your e-cigarette make you nauseous? 1 2 3 4 5 6 7
11. Did using your e-cigarette immediately reduce your craving for nicotine? 1 2 3 4 5 6 7
12. Did you enjoy using your e-cigarette? 1 2 3 4 5 6 7

APPENDIX 15

Symptoms and adverse events (AE) form:

Ask and checking the box for the presence of AEs at each study visit. Report the severity of AEs by using the AE-VAS Scale. Then, report the grade of the severity below the listed AE

| | BL | Visit 1 | Visit 2 | Visit 3 |
|--------------------------------|----|--------------------------|--------------------------|--------------------------|
| 1 Nausea | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2 Vomiting | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3 Dry mouth | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4 Constipation | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5 Diarrhea | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6 Increase in appetite | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7 Anxiety | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 8 Depression | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 9 Dyspepsia | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 10 Palpitations | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 11 Insomnia | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 12 Irritability | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 13 Abnormal dreams | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 14 Headache | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 15 Dizziness | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 16 Fatigue | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 17 Vertigo | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 18 Sweating | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 19 Skin rashes | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 20 Influenza-like illness | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 21 Respiratory tract infection | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 22. Cough | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 23. Shortness of breath | | | | |
| 24. Throat irritation | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 25. Mouth rritation | | | | |

| | | | | |
|-----------|--|--|--|--|
| 26. Other | | | | |
| 27. | | | | |
| 28. | | | | |
| 29. | | | | |
| 30. | | | | |

Adverse Event-Visual Analog Scale (AE-VAS)

| Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Significant (Grade 4) | Serious (Grade 5) |
|-------------------|-----------------------|---------------------|--------------------------|----------------------|
| | | | | |

KEY

Mild (Grade 1): Mildly symptomatic, no medical intervention needed

Moderate (Grade 2): Moderately symptomatic, evaluation by PI to determine if medical intervention is necessary

Severe (Grade 3): Medically significant but not life threatening cause for an immediate referral for a medical and/or psychiatric evaluation

Significant (Grade 4): Potentially life threatening, urgent intervention needed

Death (Grade 5): Results in death; Is life-threatening; Results in inpatient hospitalization or prolongation of existing hospitalization; Results in a persistent or significant disability/incapacity.