Protocol: Systematic review of reviews

Dose-response relationship of selective serotonin reuptake inhibitor (SSRI) in the treatment of depression: Protocol for a systematic review of reviews and meta-synthesis

Background

Antidepressant prescribing continues to grow (1,2). In part this is due to the use and availability of SSRIs (3), increased long-term prescribing (4), and the use of higher doses (5-7). In Scotland, SSRI accounted for 51% of antidepressant prescriptions and 66% of defined daily doses dispensed in 2014/15 (2). There is ambiguity in guidelines regarding SSRI dose related efficacy (8,9)

Review question

Is there a dose-response relationship for SSRI in the treatment of depression?

Aim

To review previous published reviews to assess and clarify the relationship between SSRI dose efficacy, acceptability (early treatment discontinuation – drop outs) and tolerability (reported ADEs), and critically evaluate the methods previously used to examine SSRI dose-response effects for the treatment of depression in adults.

Method

Search strategy, and criteria of eligibility and inclusion

Recommendations from the Cochrane Handbook for Systematic Reviews of Interventions informed the design of this systematic review (10). The predefined inclusion criteria for this systematic review and synthesis are presented according to PICOS (Population, Intervention, Comparator, Outcomes, Study design) criteria, Table 1.

Article titles and abstracts will be screened for inclusion. Subsequently, potentially relevant full-text articles from the literature search will then be screened for inclusion, using a structured process and standard terms supporting inclusion and exclusion. Studies that do not meet the criteria outlined above were excluded.

Reviews were excluded that involved children and adolescents aged <18 years with depression, as this cohort demonstrate variable antidepressant response rates possibly due to differences in neural development (11) and are not routinely treated in primary care by general practitioners. Reviews including older people with dementia were excluded as antidepressants are known to be of questionable benefit for depressive symptoms in this cohort (12). Additional exclusions included: depression during pregnancy, perinatal or postnatal; bipolar; concomitant psychiatric disorders, people who use drugs, concomitant opioid replacement therapy and/or co-morbidity.

Table 1 PICOS inclusion criteria	
Population	• Adult human ≥18 years old • Major depressive disorder
Intervention	• Monotherapy • Selective serotonin re-uptake inhibitors (SSRI): escitalopram, citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline
Comparison	• Placebo • SSRI
Outcome	• Antidepressant response • Efficacy: reduction in depression signs and symptoms • Acceptability: early treatment discontinuation • Tolerability: any reported adverse drug effects
Study design	• Dose-response • Review • Narrative review • Systematic review • Meta-analysis • Meta-regression • Network meta-analysis

Reviews assessing SSRI monotherapy for the treatment of depression for all licensed SSRIs were included: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. The SSRI zimelidine was not included as it has been withdrawn from the market as Guillain-Barré syndrome was associated with its use (13). Antidepressants outwith the SSRI class with novel serotonin or mixed receptor effects were excluded: vortioxetine a direct modulator of serotonergic receptor activity and inhibitor serotonin re-uptake; vilazodone with mixed SSRI and buspirone-like activity; the SNRIs venlafaxine and duloxetine; and clomipramine a TCA (14-16).

Reviews examining concomitant combination treatments: using two or more antidepressants; psychotropic and non-psychotropic medicine augmentation strategies; antidepressant with psychotherapies; and switching antidepressant studies were excluded as these strategies can be more effective than monotherapy and may be reserved for treatment resistant depression (8, 17). As the majority of national guidelines (8, 9) and drug licenses recommend standard starting doses (14) which are routinely prescribed in practice (6, 18-21) and represent standardised DDD as defined by the WHO (22), Table 2. It was considered appropriate to assess baseline standardised comparator doses to assess effects against placebo and higher SSRI doses.

Table 2. Serotonin re-uptake inhibitor defined daily doses

	Daily dose (mg)	Defined daily dose*
Escitalopram	10	1
Citalopram	20	1
Fluoxetine	20	1
Fluvoxamine	50	0.5
Paroxetine	20	1
Sertraline	50	1

*As defined by the World Health Organization.

Data sources

The following electronic databases will be searched: Embase, Medline, PsycINFO, Scopus and Cochrane Collaboration library. We will search for reviews by scrutinising and hand-searching reference lists of national and international depression treatment guidelines, and study reference lists.

As fluoxetine studies were first published in the mid 1970's and it is the SSRI that has been available on the market for the longest period (23); 1975 was used as the start date until the end of December 2020. Reviews were limited to English language

Data extraction

The following data will be extracted for each review article using a structured standardised data collection form specifically designed for this systematic review (Appendix 1). Review characteristics (e.g. lead author; type of review; protocol driven review; patient-level data or not; type of depression being treated; review setting primary or secondary care, etc.), antidepressant and comparator information (e.g. SSRI used; fixed or flexible dose study; placebo controlled; dose standardisation technique; treatment duration; etc.), and dose-response effects (e.g. efficacy, dropouts and ADEs).

Risk of bias assessment

Each review article was assessed according to the Risk of Bias in Systematic Reviews (ROBIS) tool (24), in line with Cochrane recommendations (10). Reviews were assessed using ROBIS by myself and checked by one of my supervisors. The ROBIS tool has been specifically developed and designed to assess reviews within health care settings: interventions, diagnosis, prognosis and etiology. The tools is completed in three phases: 1) assessment of relevance, 2) identify concerns with the review process and 3) judge risk of bias. Phase 2 covers four domains: study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis of findings. Phase 3 assesses overall risk of bias (low, high, unclear) from interpretation of review findings, and considers limitations identified in any of the phase 2 domains (24).

Data analysis, synthesis, and ethics

As different rating scales are used in primary studies (25) and a range of review techniques and meta-analytical approaches may have been used in reviews, the synthesis may require meta-synthesis rather than a meta-analysis (26, 27).

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Appendix 1

Article (Reference)	
Indication	
Antidepressants	
Efficacy & Dose	
ADEs (Dropouts)	
Review type (Syst, M-A, etc.)	
Protocol	
Placebo included	
Patient-level	
Flexible dose	
Dose standardisation	
Study duration	
Primary/secondary care	
Comment	