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Benzodiazepines: the time for systematic change is now

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Schmitz has written an important and timely editorial which concerns itself with the risks of this widely used group of drugs and the, largely unsuccessful, strategies to reduce consumption (1).

Prescribers and authors of guidelines from UK Royal Colleges and Government acknowledge the challenge of responding helpfully for a solution to anxiety, stress, sleeplessness and dependency and the risks of causing harm. One of the many paradoxes for prescribers is the subjective evidence of the benefits of these drugs set against the warnings, and sometimes threats, of supplying an inappropriate treatment.

The editorial highlights the risks and the failure of interventions to reduce supply are clearly articulated. The risks, however, are not supported by the cited articles which mainly conclude that evidence of dementia and cognitive decline in long term use are not proven (2, 3). Similarly, evidence of efficacy in treatment beyond the first two weeks remains unknown, largely from lack of adequate research. As Prof Malcolm Lader, the doyen of benzodiazepine research for years, observes in his important monograph, the risk benefit of the benzodiazepines remains positive in most patients in the short term. He also observes, as others in the cited papers do, that the problems and benefits are unestablished beyond that time largely because the research has never been done. The main difficulties, Lader and others have concluded, are preventing short term use extending into dependence and the characteristics of withdrawal (4).

These, are the risks for patients, and prescribers. The efficacy in acute situations, anxiety, short term sleeplessness and situational crises is accepted and based on good evidence. Evidence for the benefits in the longer term is poor and contradictory leading to difficulty for

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prescribers who listen to a constant and persistent demand. Continued use beyond the short term period has to be balanced against the risk of associated adverse effects (5).

Prescribing benzodiazepines in older patients clearly has associated risks but perhaps the most demanding and topical issues are the drug dependency and association with drug-related deaths. In Scotland, where drug-related death rates are amongst the highest per capita in the world, benzodiazepines were involved in 70% of such cases in 2019 compared with 20% in 2014. Etizolam was involved in 85% of the benzodiazepine-related deaths in Scotland in 2019 (6). In the space of a decade, the street market for benzodiazepines has shifted from one of mainly diverted prescriptions to one of illicitly manufactured drugs, thus increasing the 'risk environment' for users (7). Minimising harm in these circumstances is a challenge. The evidence for cognitive decline is undoubtedly a concern (8, 9) but this needs to be balanced against the danger of a drug-related death.

More research is needed to establish the risk of cognitive loss and dementia and, crucially, to unravel the relationship between perceived benefit and harm and the value, if any, of longer term use. Growing illicit supplies and self administration with extraordinary doses make clinical practice and evidence based harm reduction impossible to rationalise. Are we prescribing too much, or perhaps, too little?

1. Schmitz A. Benzodiazepines: the time for systematic change is now. *Addiction*. 2021;116(2):219-21.
2. Nader D, Gowing L. Is Long-Term Benzodiazepine Use a Risk Factor for Cognitive Decline? Results of a Systematic Review. *J Addict*. 2020;2020:1569456.
3. Kurko TAT, Saastamoinen LK, Tähkää S, Tuulio-Henriksson A, Taiminen T, Tiihonen J, et al. Long-term use of benzodiazepines: Definitions, prevalence and usage patterns – a systematic review of register-based studies. *European Psychiatry*. 2015;30(8):1037-47.
4. Lader M. Benzodiazepines revisited--will we ever learn? *Addiction*. 2011;106(12):2086-109.
5. Murphy Y, Wilson E, Goldner EM, Fischer B. Benzodiazepine Use, Misuse, and Harm at the Population Level in Canada: A Comprehensive Narrative Review of Data and Developments Since 1995. *Clin Drug Investig*. 2016;36(7):519-30.
6. Nielsen S, McAuley A. Etizolam: A rapid review on pharmacology, non-medical use and harms. *Drug and Alcohol Review*. 2020;39(4):330-6.
7. Rhodes T. Risk environments and drug harms: a social science for harm reduction approach. *Int J Drug Policy*. 2009;20(3):193-201.
8. Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study. *Bmj*. 2014;349:g5205.
9. Barker M, Greenwood K, Jackson M, Crowe S. Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: A meta-analysis. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists*. 2004;19:437-54.