ARTICLE

The devil is in the detail: a critique of nine editorials published by the International Task Force on Benzodiazepines

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SUMMARY

Since 2018, the International Task Force on Benzodiazepines (ITFB), a group of academic psychiatrists and academic psychologists, has advocated that clinical guidelines should change to promote benzodiazepines from second- to first-line treatment for anxiety disorders, accept their use as maintenance treatment for anxiety conditions (in particular, panic disorder) and increase their use in gastrointestinal disorders. There is merit in much of what the ITFB argues, but in this article I analyse four major claims it has made in opinion editorials that I believe are not fully supported by the available evidence.

LEARNING OBJECTIVES

After reading this article you will be able to:

- discuss the nuances of the current benzodiazepines versus antidepressant debate as it relates to their use in anxiety conditions
- recognise some of the underlying determinants that contribute to benzodiazepine utilisation rates in epidemiological data
- identify the inherent limitations that may make 'editorial' style biomedical journal articles less than authoritative for recommending widespread practice change.

KEYWORDS

Benzodiazepines; primary care; anxiety disorders; epidemiology; sleep disorders.

In 2018 the formation of the International Task Force on Benzodiazepines (ITFB) was announced in the journal *Psychotherapy and Psychosomatics* (Balon 2018). The group, comprising approximately 13 academic psychiatrists and 2 academic psychologists, have frequently contested the placement of benzodiazepines in the pharmacotherapeutic toolkit of clinicians treating anxiety illnesses. In eight editorials they have advocated for a change in clinical practice guidelines to make benzodiazepines a first-line rather than second-line treatment and for acceptance of their long-term use in anxiety conditions (panic disorder in particular) (Balon 2018, 2020, 2022; Nardi 2018, 2022; Silberman 2021, 2022; Starcevic 2022). A ninth editorial argues for the expansion of the use of benzodiazepines in gastrointestinal disorders (Balon 2021). Although much of what they argue holds merit there is equally much that deserves a more careful analysis for a medical and scientific audience to be fully persuaded by these opinion editorials. This analysis will attend only to the most important claims made by the ITFB that I believe are not fully supported by the available evidence.

Although I believe that the following four major claims are accurately derived from their editorials, I leave it to the reader to decide, after a fair reading of the editorials themselves, whether I am attacking a 'straw-man' mischaracterisation of their viewpoints (Balon 2018, 2020, 2021, 2022; Nardi 2018, 2022; Silberman 2021, 2022; Starcevic 2022).

Box 1 outlines four major claims that I have distilled from the nine ITFB editorials. I shall now examine these claims one by one, in my perceived order of their importance.

Counter-arguments to claims made by the ITFB

1 Newer antidepressants have not been shown to be superior to benzodiazepines and, given their negative adverse effect profiles as well, should not be given priority over benzodiazepines in clinical practice guidelines

There is significant overlap in the six editorials making this claim (Balon 2018, 2020; Nardi 2018, 2022; Silberman 2021; Starcevic 2022) and advocating essentially that guidelines should be revised in order to 'return to the evidence' (Silberman 2021). One of the most compelling points made by the ITFB to support this claim is that there are few large head-to-head randomised controlled trials (RCTs) comparing benzodiazepines with newer

BOX 1 Major claims derived from editorials by the International Task Force for Benzodiazepines

1 Newer antidepressants have not been shown to be superior to benzodiazepines and, given their negative adverse effect profiles as well, should not be given priority over benzodiazepines in clinical practice guidelines (Balon 2018, 2020; Nardi 2018, 2022; Silberman 2021; Starcevic 2022).
2 There is an abundance of scientific bias and unjustifiable propaganda against benzodiazepines that has prevailed in influencing guidelines and clinical practice and this has resulted in 'fear' of benzodiazepines and underuse in situations where they would be beneficial (Balon 2018, 2022; Nardi 2022; Silberman 2022).
3 The high rate of use of benzodiazepines is evidence that the guidelines should be changed to reflect real-world utilisation rates (Balon 2020, 2022; Silberman 2022; Starcevic 2022).
4 'The role of [benzodiazepines] in the management of various troublesome GI symptoms (e.g., aerophagia and GI pain), or some acute and chronic GI disorders (e.g., peptic ulcer disease, colitis and IBS), has not been fully appreciated. Their use should be expanded' (Balon 2021).

antidepressants. Given that both drug classes have been shown to be efficacious in multiple pre-marketing placebo-controlled trials, it is their contention that the drug classes should be treated equally in guideline recommendation placements (i.e. first line versus second line).

Efficacy comparison in RCTs

A 2016 Cochrane evaluation (the third comparison in the full report – selective serotonin reuptake inhibitors (SSRIs) versus benzodiazepines; Bighelli 2016) found only one industry-sponsored RCT worthy of inclusion, comparing alprazolam with paroxetine in 226 people over a 10-week period. This trial (GSK-29060/1; Glaxo Smith Kline, no date) is unpublished and it is difficult to find information on it beyond that given in the Cochrane publication itself. Nonetheless, Bighelli et al found that the trial data showed no difference between alprazolam and paroxetine on all outcomes except depression (advantage to paroxetine).

Another direct comparison study that was not included by the Cochrane group because of the design limitation of it being open-label and of higher risk for bias was that of Nardi et al, comparing clonazepam and paroxetine (Nardi 2012). This study has been cited a number of times in support of the ITFB's arguments in their editorials (the lead author of the study is a member of the ITFB) to justify longer-term use and demonstrate, at minimum, non-inferiority in effectiveness and tolerability between antidepressants and benzodiazepines (Nardi 2018, 2022; Starcevic 2022). This study is important because of the long follow-up time and it does contribute to the evidence on the topic in spite of its lack of masking ('blinding'). However, an important limitation that needs to be acknowledged is the drug selection in the trial. Clonazepam is a long half-life benzodiazepine with lesser potential for withdrawal symptoms than other benzodiazepines. In contrast, paroxetine is an SSRI with one of the shortest half-lives, thus making it more likely for withdrawal phenomena to emerge. Paroxetine has become a highly unpopular SSRI because of its higher frequency of withdrawal symptoms (Fava 2015). Additionally, its higher antimuscarinic burden makes it a less acceptable option in older adults (American Geriatrics Society Beers Criteria® Update Expert Panel 2019). It would seem that the decks were stacked in favour of the benzodiazepines in this trial in terms of drug selection. This does not invalidate the trial as an important contributor to the evidence base, but it is important to allow for the results to be read in the context of what is known about the relative differences between antidepressants and what would be a 'fair' comparator in a benzodiazepines versus antidepressant RCT if one were conducted today.

Although there is a limited number of direct head-to-head trials comparing benzodiazepines with standard first-line antidepressants, the abundance of placebo-controlled trials does enable some inferences from the overall evidence for these two medication classes via indirect comparison. It should be noted that the potential differences in trial populations and methodology between the drug classes overall warrants caution in interpretation. Nevertheless, I have compared the Cochrane systematic review of benzodiazepines versus placebo (Breilmann 2019) with that of SSRIs versus placebo (Bighelli 2018), both in the context of panic disorder treatment, and reproduced their main meta-analytic findings along with their evidence appraisal ratings Table 1.

As can be seen by a meta-analytic comparison using a standard, rigorous methodology from an internationally respected clinical research collaborative, benzodiazepines do appear to have higher effect sizes and greater tolerability on the most broadly meaningful clinical measures. However, this can be

TABLE 1 Meta-analytic comparisons of outcomes against placebo for trials of benzodiazepines and selective serotonin reuptake inhibitors in panic disorder[a]

	Anticipated absolute effect (95% CI)	Relative effect ratio (95% CI)	Number of participants (studies included)	Trial publication range, years	Average trial duration (range), weeks[b]	Certainty of evidence (GRADE)
Efficacy in terms of response						
Benzodiazepines	679 per 1000 (572–807)	1.65 (1.39–1.96)	2476 (16 RCTs)	1989–2003	6.75 (4–15)	Low
SSRIs	592 per 1000 (545–635)	1.33 (1.19–1.49)	4000 (21 RCTs)	1990–2011	10 (8–12)	Low
Efficacy in terms of remission						
Benzodiazepines	651 per 1000 (558–760)	1.61 (1.38–1.88)	2907 (15 RCTs)	1989–2000	7.66 (5–15)	Low
SSRIs	549 per 1000 (510–582)	1.23 (1.14–1.33)	3339 (16 RCTs)	1993–2007	10.25 (8–12)	Moderate
Drop-out due to adverse effects						
Benzodiazepines	65 per 1000 (47–88)	1.58 (1.16–2.15)	3263 (14 RCTs)	1990–1999	6.36 (4–10)	Low
SSRIs	97 per 1000 (77–121)	1.45 (1.16–1.81)	4131 (22 RCTs)	1990–2011	10 (8–12)	Moderate

SSRI, selective serotonin reuptake inhibitor; RCT, randomised controlled trial; GRADE, Grading of Recommendations Assessment, Development and Evaluation.
a. Data derived from two Cochrane systematic reviews: Bighelli et al (2018) and Breilmann et al (2019).
b. Some RCTs comparing antidepressants other than SSRIs with placebo in panic disorder reported by Bighelli et al (2018) lasted for up to 6 months. This table covers only SSRIs to reduce confounding and because of their continued representativeness as a subclass of first-line antidepressants in psychiatry.

at least partially accounted for by the following: (a) the rapid induction of anxiolysis compared with antidepressants would presumably result in a faster symptom reduction response, which would prevent fair comparison of the two drug classes because of early drop-outs resulting from patient-perceived 'lack of efficacy' (DeVane 2016); (b) a potentially lower standard of methodological rigour in trial design or reporting quality required for market approval in trials conducted before the advent of the modern antidepressant era might bias results towards positive outcomes; and (c) the smaller total sample sizes in the meta-analytic estimates (generally speaking, as trials accumulate, effect estimates tend to approach a smaller 'true' value).

Of importance aside from measures of effectiveness is the acknowledgement that antidepressants (at least for the SSRIs in Table 1) seem to have more trials with more participants, tend to be longer on average, have higher certainty of evidence on some measures and were conducted more recently (whether this last observation correlates with methodological rigour, however, is up for scrutiny).

Safety and tolerability

The ITFB has addressed the topic of withdrawal symptoms for benzodiazepines and antidepressants and correctly draws attention to the bias in clinical language that has traditionally accompanied these drug classes in this regard ('discontinuation' symptoms for antidepressants and 'withdrawal' symptoms for benzodiazepines). The increasing recognition of and research on 'withdrawal' symptoms from antidepressant discontinuation has been acknowledged in a position statement from the Royal College of Psychiatrists as well as a guidance document from the National Institute for Health and Care Excellence (NICE) that is in conformity with the ITFB on possibly questioning the merits of routine, long-term use of antidepressants (particularly in cases of mild symptom presentation) (Royal College of Psychiatrists 2019; National Institute for Health and Care Excellence 2022).

Reviews have described a very similar range of withdrawal symptoms and potential time course for these symptoms for both benzodiazepines and antidepressants (Nielsen 2012; Cosci 2020). However, an earlier direct comparison study of withdrawal symptoms, using validated patient-assessment instruments measuring dependency and withdrawal (the only one of its kind on the subject, to my knowledge), was oddly not included in these two reviews but nevertheless demonstrated that benzodiazepines show greater dependence potential than antidepressants and may have more significant withdrawal severity, although this latter finding was not statistically significant (van Broekhoven 2002). Another important clinical consideration that must not be overlooked is the significant differences between antidepressants in both their pharmacokinetics and pharmacodynamics. This enables clinicians to individualise the selection of antidepressant to avoid particular types of adverse effect for a given patient in a way that is comparatively restricted in benzodiazepine selection.

Also relevant to the clinical discussion is the issue of major adverse incidents such as motor vehicle accidents and falls leading to fractures (Brandt 2017). This topic is either omitted from discussion or glossed over briefly by the ITFB in its editorial opinion work, despite the public health and safety significance. In the case of driving, some evidence syntheses show that there is significantly more risk of injury or fatality with benzodiazepines than with antidepressants (Elvik 2013; Rudisill 2016). This is not to state that antidepressants are completely

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devoid of risk, but both the experimental and epidemiological evidence clearly shows a strong case for caution for benzodiazepine use in people who drive vehicles (Brandt 2017).

In the case of risk of bone fracture due to falls, many psychotropic medications (not just benzodiazepines) contribute substantially to this important public health concern (Seppala 2018). A number of studies have concluded that SSRIs may pose a greater hazard than benzodiazepines in this regard (Rabenda 2013; Bolton 2017).

Final point

As one can hopefully appreciate, an updated, comprehensive, evidence-based comparison between modern antidepressants and benzodiazepines on a number of important outcomes would be required by a panel of guideline experts to either confirm or change the relative placement of these medications in the prescriptive recommendations for anxiety illnesses. Nine editorials, no matter how well-written, should not suffice to change routine clinical pharmacotherapy decision-making at this time.

2 There is an abundance of scientific bias and unjustifiable propaganda against benzodiazepines that has prevailed in influencing guidelines and clinical practice and that this has resulted in 'fear' of benzodiazepines and underuse in situations where they would be beneficial

I agree with the authors (Balon 2018, 2022; Nardi 2022; Silberman 2022) that conflicts of interest, via the pharmaceutical industry, influencing the production of educational content, research and clinical guidelines is a real concern and threat to medical decision-making whereby the best available evidence becomes suppressed or distorted. However, the overwhelming degree of concordance between various national and international guidelines on the point of antidepressants having some precedence over benzodiazepines as a first-line maintenance treatment in anxiety conditions should not be simply dismissed as a grand conspiracy of conflict of interest. I contend that a full systematic review of the literature with the purpose of analysing claims about benzodiazepines should be conducted to firmly convince the clinical scientific community of indisputable, persisting bias that has distorted the scientific record. Ultimately, the burden of proof remains on the ITFB to demonstrate, in a compelling, methodologically rigorous way, that benzodiazepines deserve a place alongside modern antidepressants as a first-line maintenance treatment for common anxiety disorders. The group's call for new head-to-head RCTs is a good starting point.

I also wish to respectfully draw attention to the fact that six of the nine editorials (Balon 2018, 2021, 2022; Nardi 2022; Silberman 2022; Starcevic 2022) are in the journal *Psychotherapy and Psychosomatics*, whose current editor-in-chief is a member of the ITFB. The current editor-in-chief and both associate editors of the journal are also from Italy, the country identified by the International Narcotics Control Board as being responsible for over 50% of global pharmaceutical production of benzodiazepines in 2020 (International Narcotics Control Board 2021). In good faith I expect this to be purely coincidental. However, a country that has an economic interest in the export and clinical use of millions of doses of benzodiazepines may produce a widespread clinical environment in which these medications are more favourably viewed than elsewhere in the world. I hope that at the minimum, a group rightfully drawing attention to industry bias as regards antidepressants shall itself set a higher future standard by publishing its opinion editorials in a peer-reviewed journal that is not associated with the ITFB. This would reduce the appearance of privileging particular perspectives or agendas. Such an approach is consistent with already well-established ethical publication standards for biomedical journals (Gottlieb 2017; Stead 2017).

3 The high rate of use of benzodiazepines is evidence that the guidelines should be changed to reflect real-world utilisation rates

I contest that pharmacoepidemiological data showing a rise in benzodiazepines use (Balon 2020, 2022; Silberman 2022; Starcevic 2022) is too complicated a matter to warrant a simple claim that the majority of real-world use 'must be ahead of treatment guidelines in this realm' (Starcevic 2022). Although we might hope to have such faith in prescribers, it is clear that there are a number of reasons why guidelines may not be adhered to, some of which are described here.

First, adherence to practice guidelines is a problem in many fields of medicine and healthcare and is the daunting task of an entire domain of research and healthcare work: implementation science research and knowledge translation effort (Eccles 2006; Straus 2013). It does not follow that simply because real-world practice is very imperfect guidelines should 'go backwards' to match it. Indeed, research is currently ongoing to improve the success of de-prescribing in the context of long-term benzodiazepine use by using implementation science methods, theories and frameworks (Lynch 2022).

Second, in many instances the prescribing of benzodiazepines rather than antidepressants is more stressful for both patient and clinician. Many patients are worried about the significant withdrawal syndrome associated with benzodiazepines. Also, there are strict regulatory requirements in most jurisdictions for the prescribing and dispensing of benzodiazepines, which create a difficult situation for patients taking these drugs long-term who either lose their medication or who independently increase dosage or frequency beyond that prescribed. Their doctors must submit early dispensing authorisations to pharmacists for them to provide the medication for patients who have run out of their benzodiazepines earlier than expected. This is not an uncommon scenario in clinical practice and contributes to the reluctant long-term prescribing of benzodiazepines on the part of some treating clinicians. The imposition placed on busy prescribers by the urgent demand for 'early release' authorisations by patients and their pharmacists is made difficult by the inability to assess the patient in a timely manner to guide prescribing decisions. The stress placed on relationships between patients and clinicians because of both the nature of benzodiazepine dependence and the medication access restrictions is not to be underestimated (Sirdifield 2013, 2016). It is unclear what the ITFB's position is on the scheduling or regulatory status of benzodiazepines and what changes, if any, it believes should be made. Overall, in this regard, I would argue that antidepressants are frequently less complex and socially concerning, in terms of patients' medication behaviour, for the stability of the average prescriber–patient relationship, an important factor in and of itself for the quality provision of care.

Third, much out-patient benzodiazepine use is for insomnia, a condition where the benefit/risk ratio diminishes with long-term use, and benzodiazepines are not recommended over cognitive–behavioural therapy for chronic insomnia (Sateia 2016). Insomnia as an explanation or argument for greater benzodiazepine use is conveniently left out of these editorials, perhaps because some evidence has shown that benzodiazepines can diminish sleep quality (Bourgeois 2013). A different type of study that conducted a qualitative evaluation of factors affecting patient preference found a significant association between patients using benzodiazepines for chronic insomnia and a later desire to taper off the medication (Sake 2019). Furthermore, misuse of benzodiazepines by a patient struggling with insomnia may also then lead to subsequent confrontational encounters with care providers because of the regulatory requirements described in the previous point.

4 'The role of [benzodiazepines] in the management of various troublesome GI symptoms (e.g., aerophagia and GI pain), or some acute and chronic GI disorders (e.g., peptic ulcer disease, colitis and IBS), has not been fully appreciated. Their use should be expanded.' (Balon 2021)

Although Balon et al's (2021) editorial provides an interesting overview of potential pharmacological mechanisms, a review of the link between various gastrointestinal (GI) disorders and mental illness (especially somatic disorders such as irritable bowel syndrome (IBS)) and a short review of a few studies from the 1970s, the authors do not come close to justifying the above concluding statement. In a section just short of 500 words they cover the efficacy of benzodiazepines for various GI conditions. The section briefly reviews six studies from the 1970s, five of which are small and none of which have influenced recent gastroenterology clinical practice guidelines in support of benzodiazepines in routinely supplanting commonly used medication classes such as antispasmodics, antidepressants or proton pump inhibitors (Kamada 2021; Lacy 2021). Although not specifically addressed, the unique but antiquated combination of chlordiazepoxide and clidinium bromide was recently evaluated with positive results as an add-on therapy for functional dyspepsia but it is unclear how much benefit is clearly derived from the antimuscarinic compared with the benzodiazepine, as they have not been evaluated separably (Puasripun 2020). The authors of this trial recommend short-term use of this combination solely as an adjunct to standard pharmacotherapy such as proton pump inhibitors (Puasripun 2020).

Before their concluding statement, Balon et al (2021) make quite reasonable points for preferring benzodiazepines over antidepressants based on their respective GI adverse effect profiles. It should be noted that benzodiazepines are not entirely devoid of GI concerns themselves, in particular oesophageal acid reflux (Tutuian 2010), a point that was missed by the authors. Although their arguments here would be most relevant for the condition of IBS, a comparative review of the positive evidence for SSRIs in IBS is not mentioned and it is summarily concluded that benzodiazepines should therefore be preferred.

Closing remarks

When it comes to interpretation of psychiatric evidence, there are numerous ways in which clinicians can fall prey to one of the many forms of bias (Makhinson 2012). As with many controversial issues in science and medicine, I believe that the truth about benzodiazepines and antidepressants rests somewhere between two competing schools of thought. I agree with the ITFB authors on many

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points in their well-written editorials and feel that they do an important job in discussing *some* truth about benzodiazepines and antidepressants in their arguments. However, I feel that it is of benefit to readers to demonstrate a different perspective on the evidence. Ultimately, readers are reminded that brief editorials showcasing 'expert opinion' and not subject to a clear methodology are the lowest form of evidence and are subject to problems such as citation bias (Jannot 2013). I acknowledge that this critique itself is also potentially prone to such biases, but I hope that it has aided in balancing the dialogue for the readers of the ITFB's work.

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J.B. is the only author of this work and is accountable for all aspects of the work.

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J.B. serves on an advisory panel to the Alliance for Benzodiazepine Best Practices, a not-for-profit organisation with the 'primary objective to significantly reduce the number of benzodiazepine withdrawal sufferers by reducing the number of new prescriptions for benzodiazepines and Z-drugs, limit the duration of use, and provide an evidence-based pathway for deprescribing. [Its] focus is to illustrate the problems associated with benzodiazepines, illuminate alternatives to their use, and provide tools for clinicians to assist benzodiazepine withdrawal syndrome sufferers' (Alliance for Benzodiazepine Best Practices 2022).

References

Alliance for Benzodiazepine Best Practices (2022) *About Us*. Alliance for Benzodiazepine Best Practices (https://benzoreform.org/about-us). Accessed 18 Jun 2022.

American Geriatrics Society Beers Criteria® Update Expert Panel (2019) American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society*, **67**: 674–94.

Balon R, Chouinard G, Cosci F, et al (2018) International Task Force on Benzodiazepines. *Psychotherapy and Psychosomatics*, **87**: 193–4.

Balon R, Starcevic V, Silberman E, et al (2020) The rise and fall and rise of benzodiazepines: a return of the stigmatized and repressed. *Brazilian Journal of Psychiatry*, **42**: 243–4.

Balon R, Sonino N, Rafanelli C (2021) Benzodiazepines' role in managing gastrointestinal disorders. *Psychotherapy and Psychosomatics*, **90**: 81–4.

Balon R (2022) Who's afraid of benzodiazepines?. *Psychotherapy and Psychosomatics*, **91**: 291–4.

Bighelli I, Trespidi C, Castellazzi M, et al (2016) Antidepressants and benzodiazepines for panic disorder in adults. *Cochrane Database of Systematic Reviews*, **9**(9): CD011567.

Bighelli I, Castellazzi M, Cipriani A, et al (2018) Antidepressants versus placebo for panic disorder in adults. *Cochrane Database of Systematic Reviews*, **4**(4): CD010676.

Bolton JM, Morin SN, Majumdar SR, et al (2017) Association of mental disorders and related medication use with risk for major osteoporotic fractures. *JAMA Psychiatry*, **74**: 641–8.

Bourgeois J, Elseviers MM, Van Bortel L, et al (2013) Sleep quality of benzodiazepine users in nursing homes: a comparative study with nonusers. *Sleep Medicine*, **14**: 614–21.

Brandt J, Leong C (2017) Benzodiazepines and Z-drugs: an updated review of major adverse outcomes reported on in epidemiologic research. *Drugs in R&D*, **17**: 493–507.

Breilmann J, Girlanda F, Guaiana G, et al (2019) Benzodiazepines versus placebo for panic disorder in adults. *Cochrane Database of Systematic Reviews*, **3**(3): CD010677.

Cosci F, Chouinard G (2020) Acute and persistent withdrawal syndromes following discontinuation of psychotropic medications. *Psychotherapy and Psychosomatics*, **89**: 283–306.

DeVane CL (2016) Clinical pharmacokinetics and pharmacodynamics of anxiolytics and sedative/hypnotics. In *Applied Clinical Pharmacokinetics and Pharmacodynamics of Psychopharmacological Agents* (eds MW Jann, SR Penzak, LJ Cohen): 247–66.

Eccles MP, Mittman BS (2006) Welcome to implementation science. *Implementation Science*, **1**(1): 1–3.

Elvik R (2013) Risk of road accident associated with the use of drugs: a systematic review and meta-analysis of evidence from epidemiological studies. *Accident Analysis and Prevention*, **60**: 254–67.

Fava GA, Gatti A, Belaise C, et al (2015) Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. *Psychotherapy and Psychosomatics*, **84**: 72–81.

Glaxo Smith Kline (no date) *A* Double-Blind, Multicenter, Flexible-Dose Study *of* Paroxetine, Alprazolam *and* Placebo *in the* Treatment *of* Panic Disorder (*GSK-29060*/1). GSK Clinical Studies Register. Available from: http://www.gsk-clinicalstudyregister.com/.

Gottlieb JD, Bressler NM (2017) How should journals handle the conflict of interest of their editors? Who watches the "watchers"? *JAMA*, **317**: 1757–8.

International Narcotics Control Board (2021) *Psychotropic Substances 2021: Statistics for 2020 (Technical Report)*. United Nations.

Jannot A-S, Agoritsas T, Gayet-Ageron A, et al (2013) Citation bias favoring statistically significant studies was present in medical research. *Journal of Clinical Epidemiology*, **66**: 296–301.

Kamada T, Satoh K, Itoh T, Ito M, et al (2021) Evidence-based clinical practice guidelines for peptic ulcer disease 2020. *Journal of Gastroenterology*, **56**: 303–22.

Lacy BE, Pimentel M, Brenner DM, et al (2021) ACG clinical guideline: management of irritable bowel syndrome. *American Journal of Gastroenterology*, **116**: 17–44.

Lynch T, Ryan C, Cadogan CA (2022) "I just thought that it was such an impossible thing": a qualitative study of barriers and facilitators to discontinuing long-term use of benzodiazepine receptor agonists using the theoretical domains framework. *Health Expectations*, **25**: 355–65.

Makhinson M (2012) Biases in the evaluation of psychiatric clinical evidence. *Journal of Nervous and Mental Disease*, **200**: 76–82.

Nardi AE, Freire RC, Mochcovitch MD, et al (2012) A randomized, naturalistic, parallel-group study for the long-term treatment of panic disorder with clonazepam or paroxetine. *Journal of Clinical Psychopharmacology*, **32**: 120–6.

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Nardi AE, Cosci F, Balon R, et al (2018) The prescription of benzodiazepines for panic disorder: time for an evidence-based educational approach. *Journal of Clinical Psychopharmacology*, **38**: 283–5.

Nardi AE, Quagliato LA (2022) Benzodiazepines are efficacious and safe for long-term use: clinical research data and more than sixty years in the market. *Psychotherapy and Psychosomatics*, **91**: 300–3.

National Institute for Health and Care Excellence (2022) *Medicines* Associated *with* Dependence *or* Withdrawal Symptoms: Safe Prescribing *and* Withdrawal Management *for* Adults (NICE Guideline *NG215*). NICE.

Nielsen M, Hansen EH, Gøtzsche PC (2012) What is the difference between dependence and withdrawal reactions? A comparison of benzodiazepines and selective serotonin re-uptake inhibitors. *Addiction*, **107**: 900–8.

Puasripun S, Thinrungroj N, Pinyopornpanish K, et al (2020) Efficacy and safety of clidinium/chlordiazepoxide as an add-on therapy in functional dyspepsia: a randomized, controlled, trial. *Journal of Neurogastroenterology and Motility*, **26**: 259–66.

Rabenda V, Nicolet D, Beaudart C, et al (2013) Relationship between use of antidepressants and risk of fractures: a meta-analysis. *Osteoporosis International*, **24**: 121–37.

Royal College of Psychiatrists (2019) *Position Statement on Antidepressants and Depression* (PS04/19). RCPsych.

Rudisill TM, Zhu M, Kelley GA, et al (2016) Medication use and the risk of motor vehicle collisions among licensed drivers: a systematic review. *Accident Analysis and Prevention*, **96**: 255–70.

Sake FTN, Wong K, Bartlett DJ, et al (2019) Benzodiazepine usage and patient preference for alternative therapies: a descriptive study. *Health Science Reports*, **2**(5): e116.

Sateia MJ, Buysse DJ, Krystal AD, et al (2016) Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. *Journal of Clinical Sleep Medicine*, **13**: 307–49.

Seppala LJ, Wermelink AMAT, de Vries M, et al (2018) Fall-risk-increasing drugs: a systematic review and meta-analysis: II. psychotropics. *Journal of the American Medical Directors Association*, **19**(4): 371.e11–7.

Silberman E, Balon R, Starcevic V, et al (2021) Benzodiazepines: it's time to return to the evidence. *British Journal of Psychiatry*, **218**: 125–7.

Silberman EK (2022) Stigmatization of benzodiazepines: pharmacologic and nonpharmacologic contributions. *Psychotherapy and Psychosomatics*, **91**: 304–6.

Sirdifield C, Anthierens S, Creupelandt H, et al (2013) General practitioners' experiences and perceptions of benzodiazepine prescribing: systematic review and meta-synthesis. *BMC Family Practice*, **14**: 191.

Sirdifield C, Chipchase SY, Owen S, et al (2016) A systematic review and meta-synthesis of patients' experiences and perceptions of seeking and using benzodiazepines and Z-drugs: towards safer prescribing. *Patient*, **10**(1): 1–15.

Starcevic V (2022) Representation of benzodiazepines in treatment guidelines: the paradox of undesirable objectivity. *Psychotherapy and Psychosomatics*, **91**: 295–9.

Stead WW (2017) The complex and multifaceted aspects of conflicts of interest. *JAMA*, **317**: 1765–7.

Straus SE, Tetroe J, Graham ID (2013) *Knowledge Translation in Healthcare: Moving from Evidence to Practice* (2nd edn). Wiley.

Tutuian R (2010) Adverse effects of drugs on the esophagus. *Best Practice and Research: Clinical Gastroenterology*, **24**: 91–7.

van Broekhoven F, Kan CC, Zitman FG (2002) Dependence potential of antidepressants compared to benzodiazepines. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **26**: 939–43.

MCQs

Select the single best option for each question stem

1 According to Cochrane systematic reviews of the placebo-controlled RCT evidence on the attainment of clinical remission in panic disorder with the use of SSRIs and benzodiazepines:

a benzodiazepines have smaller effect sizes but higher-quality trial evidence
b SSRIs have larger effect sizes and higher-quality trial evidence
c benzodiazepines have larger effect sizes but lower-quality trial evidence
d SSRIs have smaller effect sizes and lower-quality trial data
e there is no difference between benzodiazepines and SSRIs in either effect size nor quality of trial evidence.

2 Which of the following statements is not true regarding antidepressant and benzodiazepine withdrawal symptoms?

a severity of withdrawal is frequently dependent on the pharmacokinetic properties of the individual drug
b antidepressants produce a discontinuation syndrome but not withdrawal symptoms *per se*
c benzodiazepine withdrawal may present with similar symptoms as antidepressant withdrawal
d time course for withdrawal symptom presentation may overlap in many instances between benzodiazepines and antidepressants
e paroxetine may be relatively more likely to produce withdrawal symptoms sooner than clonazepam after abrupt discontinuation.

3 Which of the following least explains the complexity of benzodiazepine utilisation rates in any given jurisdiction?

a the patient's inability or unwillingness to taper their medication to discontinuation
b clinician biases in drug selection
c accessibility to psychiatric care
d the lack of pharmacies available to dispense benzodiazepines
e changing incident rates of insomnia and anxiety diagnoses.

4 The scientific and research discipline that focuses on improving the utilisation of best practice evidence in real-world settings is often referred to as:

a implementation science
b knowledge action effort
c clinical informatics
d knowledge dissemination science
e clinical practice research.

5 Which of the following statements regarding benzodiazepines is demonstrably untrue?

a benzodiazepines remain potentially useful therapeutic agents in carefully selected clinical circumstances
b benzodiazepines are devoid of major side-effects, are very effective and should therefore be used more broadly for long-term treatment in most cases of anxiety
c benzodiazepines have potential adverse effects which include drowsiness, cognitive fogging, physical dependency, memory impairment, psychomotor impairment and, uncommonly, acid reflux
d benzodiazepines produce rapid anxiolysis and/or sedation, which make them particularly useful in the acute phase treatment of anxiety and insomnia
e benzodiazepines are useful for the treatment of seizures, alcohol withdrawal and catatonia.