Prescribing and deprescribing guidance for benzodiazepine and benzodiazepine receptor agonist use in adults with depression, anxiety, and insomnia: an international scoping review

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Summary

Background Clinical practice guidelines and guidance documents routinely offer prescribing clinicians' recommendations and instruction on the use of psychotropic drugs for mental illness. We sought to characterise parameters relevant to prescribing and deprescribing of benzodiazepine (BZD) and benzodiazepine receptor agonist (BZRA), in clinical practice guidelines and guidance documents internationally, for adult patients with unipolar depression, anxiety disorders and insomnia to understand similarities and discrepancies between evidence-based expert opinion.

Methods A Scoping Review was conducted to characterize documents that offered evidence-based and/or consensus pharmacologic guidance on the management of unipolar depression, anxiety disorders, obsessive-compulsive disorders, post-traumatic stress disorders and insomnia. A systematic search was conducted of PubMed, SCOPUS, PsycINFO and CINAHL from inception to October 13, 2023 and supplemented by a gray literature search. Documents were screened in Covidence for eligibility. Subsequent data-charting on eligible documents collected information on aspects of both prescribing and deprescribing.

Findings 113 documents offering guidance on BZD/BZRA use were data-charted. Overall, documents gathered were from Asia (n = 11), Europe (n = 34), North America (n = 37), Oceania (n = 7), and South America (n = 4) with the remainder being "International" (n = 20) and not representative to any particular region or country. By condition the documents reviewed covered unipolar depressive disorders (n = 28), anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder (n = 42) and Insomnia (n = 25). Few documents (n = 18) were sufficiently specific and complete to consider as de-prescribing focused documents.

Interpretation Documents were in concordance in terms of BZD and BZRA not being used routinely as first-line pharmacologic agents. When used, it is advisable to restrict their duration to "short-term" use with the most commonly recommended duration being less than four weeks. Documents were less consistent in terms of prescriptive recommendations for specific drug, dosing and administration pattern (i.e regular or 'as needed') selection for each condition. Deprescribing documents were unanimously in favor of gradual dose reduction and patient shared decision-making. However, approaches towards dose-tapering differed substantially. Finally, there were inconsistencies and/or insufficiency of detail, among deprescribing documents, in terms of switching to a long-acting BZD, use of adjunctive pharmacotherapies and micro-tapering.

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Research in context

Evidence before this study

Guidelines have offered similar messaging around the role of benzodiazepines (BZD) and benzodiazepine receptor agonists (BZRA) for many years now. In general, this is to restrict to short-term use, when possible, to minimize acute harm associated with central nervous system depression as well as longer-term dependence. In recent years, an emphasis on safe deprescribing has also emerged as a counter-balance for ensuring appropriate medication safety in a globally aging population. A scoping review of biomedical literature databases and a gray-literature search, up to October 2023, yielded 113 clinical practice guidelines or clinical guidance documents.

Added value of this study

Our review offers the first (to our knowledge) comprehensive and internationally comparative summary of clinical guidance on the prescriptive use of BZD/BZRA for anxiety disorders, mood disorders and insomnia as well as deprescribing guidance towards BZD/BZRA discontinuation success.

Implications of all the available evidence

Broad consensus among experts was highly confirmed in regards to limiting use to the short-term when prescribing and engaging in shared decision making with gradual dose reduction for deprescribing. Areas of discrepancy in deprescribing pertain to the precise evidence for particular tapering regimens, switching to a long-acting BZD, adjunctive or substitutive non-BZD pharmacotherapy and 'micro-tapering'. These latter issues were inconsistently or insufficiently addressed thus suggesting the need for further research clarity and clearer evidence-based guidance in these areas.

Introduction

After several decades of use, Benzodiazepines and Benzodiazepine Receptor Agonists remain important therapeutic options for the treatment of mental health related concerns such as anxiety and sleep disorders.[1] Benzodiazepines (BZD) compose a class of psychoactive drugs which conform to the minimum molecular structure of fused benzene and diazepine rings. Benzodiazepine receptor agonists (BZRA), colloquially referred to as "Z-Drugs" (or occasionally by the less precise term "non-benzodiazepines"), emerged on the scene in the 1990s with early marketed messaging appeal as a safer BZD alternative. However, these agents generally share the same broadly common receptor target as conventional BZD despite having heterogenous chemical structures. The anxiolytic and sedative-hypnotic properties of these agents are characterised by positive allosteric modulation of γ-amino butyric acid (GABA)-A receptors. This agonistic activity on GABA-A receptors results in subsequent hyperpolarization of neuronal cell membranes via chloride ion influx.[2–4] Nuanced distinctions between BZD and BZRA in GABA-A receptor sub-unit binding activity accounts for differences in the indications between these drug classes and are detailed extensively elsewhere.[5]

Clinicians and patients have utilized these medications for these potent psychotropic effects for decades with utilization reaching peak popularity in the 1970's.[6] This was followed by the gradual clinical realization from accumulating evidence and experience that long-term use of BZD cause potential physiologic dependence, cognitive impairment and psychomotor impairment leading to falls and fractures.[7–9] Other more recent controversial health concerns such as dementia, cancer, pneumonia, suicidality, and complex persistent dependence, have prompted more advocacy and research in opposition to the indiscriminate, widespread, and long-term use of these agents.[9–12] Nevertheless, the issue of long-term use persists in many nations and has been prominently referred to as 'our other prescription drug problem' beyond opioids.[13,14]

The public health implications for BZD & BZRA use are continuously being revised in light-of newer pharmacoepidemiologic studies and patient engagement research both of which elucidate these issues in greater detail.[15,16]

Since the 2000's in particular, vigorous debate in the literature amongst psychiatrists and other health professionals practising within the bounds of clinical psychopharmacology has resulted in a continued division of competing perspectives about BZD related benefits and harms for different clinical circumstances.[17–19] The perspective that various guidelines on BZD prescribing have been largely concordant with one another for common mental health and sleep concerns, while commonly held among clinicians and academics, has not yet been subject to rigorous scrutiny to examine differences between recommendations and guidance from these differing groups of experts.[20] We sought to characterise parameters relevant to BZD and BZRA prescribing and de-prescribing, in clinical practice guidelines and prescribing guidance documents, for

adult patients with anxiety disorders and insomnia. The inclusion of unipolar depressive disorders in this review is relevant for applicability to common patient encounters in both primary care and psychiatry where depressive and anxiety illnesses are often either comorbid or mixed to varying extents in their symptom presentation.[21]

Methods

Overview

A systematic scoping review was conducted according to Arksey & O'Malley's methodologic guidance and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines extension for Scoping Reviews (PRISMA-ScR).[22,23] (Supplemental file 1). A scoping review is a knowledge synthesis methodology that has become increasingly popular over the past decade due to the extensiveness of the medical literature.[24] Scoping reviews seek to offer robust observations on the literature for a particular topic and differ from systematic reviews in that they do not typically utilise a rigorous quantitative or meta-analytic methodology to draw specific conclusions on intervention effectiveness or risk estimates. Because this project focused on guidelines and guidance documents, the majority of which themselves inherently used a systematic approach towards the gathering and interpretation of original research evidence by experts, a formal quality assessment of guideline recommendations was not conducted herein.

A systematic search was used to identify potential documents reporting BZD & BZRA pharmacotherapy recommendations or guidance for anxiety, depressive and sleep disorders. Retrieved articles were uploaded to Covidence for screening (https://www.covidence.org/).[25] The title and abstract screening stage was followed by a full-text screening stage. Eligibility criteria was applied loosely to title and abstract screening with preference for inclusion (if any uncertainty) and then applied directly at the full-text screening stage. Data-charting was conducted to collect information of relevance to the prescribing and de-prescribing of BZD/BZRA (Box 1).

Protocol

A protocol was registered with Open Science Framework (OSF) in summer of 2021 with minor revisions to update the definition of a 'guideline' based on team consensus prior to full-text screening and to expand the gray literature search methodology.[26] The protocol was developed in accordance with the PRISMA-P statement.[27]

Search strategy and selection criteria

A comprehensive search strategy (Supplemental file 1) was conducted on multiple biomedical literature databases including PubMed, SCOPUS, PsycINFO and CINAHL from inception of each database to Oct 27, 2022. The search was updated after peer-review to Oct 13, 2023. The search was constructed by a biomedical research librarian and it was peer-reviewed according to the Peer-Review for Electronic Search Strategy (PRESS) guidelines.[28]

The search used a combination of subject headings and keywords appropriate for each database. The terms were focused around the concepts of benzodiazepine and benzodiazepine receptor agonist; depression, anxiety and insomnia; and deprescription. Results were limited to clinical guidelines using the filter created by the Canadian Agency for Drugs, Technology, and Health (CADTH).[29] No language or date filters were used. A multi-file search was run in the Ovid databases; all results were then uploaded to Covidence for de-duplication. Lastly, a gray-literature search using Google and the CADTH gray-matters search tool was used to discover additional guidance documents on BZD/BZRA prescribing not indexed in a conventional biomedical literature database.[30] All search strategies are available via: https://doi.org/10.34990/FK2/SHQJWT.

Box 1.
Project data-charting elements.

BZD/BZRA medication management domain	Item of clinical relevance
Prescribing	Pharmacologic Option for 1st Line Treatment
	Intended initial duration of use
	Preferred BZD/BZRA agent(s) of choice
	Direction on starting doses
Deprescribing	Engagement in patient shared-decision making
	Gradual dose tapering
	Switch to long-acting BZD
	Substitutive Pharmacotherapy (Non-BZD)
	Unconventional formulation alteration tapering strategies

Abbreviations: BZD; benzodiazepine, BZRA; benzodiazepine receptor agonist.

Eligibility criteria

Documents that were included were those defined or identified as either 'clinical practice guidelines' or 'clinical guidance documents' addressing pharmacotherapy of anxiety disorders, insomnia, or unipolar depressive disorders in adults. Additionally, we included guidelines and guidance documents that were non-specific to any conditions but that remained primarily specific to BZD/BZRA related issues (BZD use disorder or deprescribing/tapering). 'Clinical practice guideline' was defined as "a collectively written document where recommendations are made, through a pre-specified evidence-based recommendation process, to an audience by a professional society, association, or group of affiliated experts on a topic relating to medical practice"

(adapted from the Institute of Medicine definition).[31] Alternatively, a 'guidance document' was originally defined by us as that which was "derived through a consultation process at a jurisdictional level to establish standards of care." Discussions were held about the difference between these types of documents between the screening reviewers to establish an informal working consensus based on an understanding of these approximate definitions before the full-text screening stage. It was agreed upon that consensus articles, disease state algorithms and other specific types of "review" articles could be eligible for inclusion if they avoided the other exclusion criteria, because they still offered important information on expert opinion and guidance for BZD/BZRA use. As such, these types of documents were categorised as "guidance" documents rather than "guidelines" per se.

Notable other record exclusions were all other review articles on BZD/BZRA or for the conditions under study, those documents specific to other psychiatric conditions such as psychotic disorders or bipolar disorders as well as those specific to pediatric or adolescent populations. Additionally, duplicate guidelines published in multiple journals, guidelines that have since been replaced by a newer version or those that offered specific prescribing guidance for a different class of medication (i.e antidepressants) were also excluded.

Screening process

Following de-duplication, two reviewers (JB & JB) systematically screened all articles over two rounds in Covidence; once in a title and abstract screening stage where the inclusion/exclusion criteria were very loosely applied (with preference towards inclusion in cases of uncertainty) and again in the full-text screening stage, wherein the eligibility criteria were more carefully applied and exclusion reasons recorded. Disagreements between reviewers were resolved by a third reviewer in the title-abstract stage and via discussion and agreement in the full-text screening stage. Proportionate agreement was 70.5% and 74% in the title-abstract and full-text screening stages, respectively, with a Cohen's kappa of 0.46 indicating moderate inter-rater reliability.

Data-charting process

Data-charting templates (in protocol) were pilot tested for face-validity on 10 representative documents selected before the search execution. Items of interest for data-charting were broadly divided into four categories and data-charted into Covidence by DN and checked for accuracy by JB (Brandt). Those items pertained to; i) characteristics of the guideline/guidance document itself ii) the patient population and condition under review iii) prescribing direction relating to initiation or maintenance of a BZD/BZRA and iv) deprescribing factors relating to discontinuation strategies for BZD/BZRA. The first two categories were analysed to understand broad trends within the guidance literature, while the latter two categories were the clinical focus of the scoping review itself.

Grey literature

Grey literature was identified, screened and data-charted by JB (Brandt) according to the eligibility criteria and pre-determined data elements. Accuracy of results were confirmed by JB (Bressi), CC, JWD and MWD.

Statistical analysis

We calculated the proportions of different responses for items relevant to the prescribing of BZD/BZRA based on either the condition being treated or the items relevant for deprescribing of a BZD/BZRA. Key characteristics of all eligible documents (regional representation, number of guidelines vs. guidance documents, and time-period of publication) were analysed by counts and proportion. This was followed by analyses by mental condition category; anxiety and related disorders, insomnia, and unipolar depressive disorders, to cover prescriptive recommendations. We similarly analysed de-prescribing focused documents separately regarding medication-based strategies for discontinuation. Lastly, to confirm the relevance and consistency of our results, we performed a sensitivity analysis check by excluding all final literature that was older than 2010.

Results

Characteristics of eligible documents

Of 3274 records screened in Covidence, 76 were clinical practice guidelines or guidance documents that met the eligibility criteria. An additional 37 records were identified from the gray-literature and retained after screening, making for a total of 113 documents that were data-charted (Fig. 1). Eighty-two (72.6%) of the documents were published in 2010 or after, 25 (22.1%) were published between 2000 and 2009 and 6 (5.3%) were published between 1990 and 1999.

Sixty-five records (57.5%) were identified as clinical practice guidelines with the remainder as guidance documents. Most guidelines and guidance documents utilised a clear and transparent consensus and evidence-based approach towards deriving their recommendations or clinical advice. However, there was much heterogeneity in the methodology between expert groups. This ranged from the explicit use of GRADE as a gold-standard (n = 18) to a completely unspecified approach (n = 22), with the remaining documents using some process of consensus with varying degrees of explicit evidence integration. Overall, documents gathered were from Asia (n = 11), Europe (n = 34), North America (n = 37), Oceania (n = 7) and South America (n = 4). However, 20 documents were "international" in scope representing

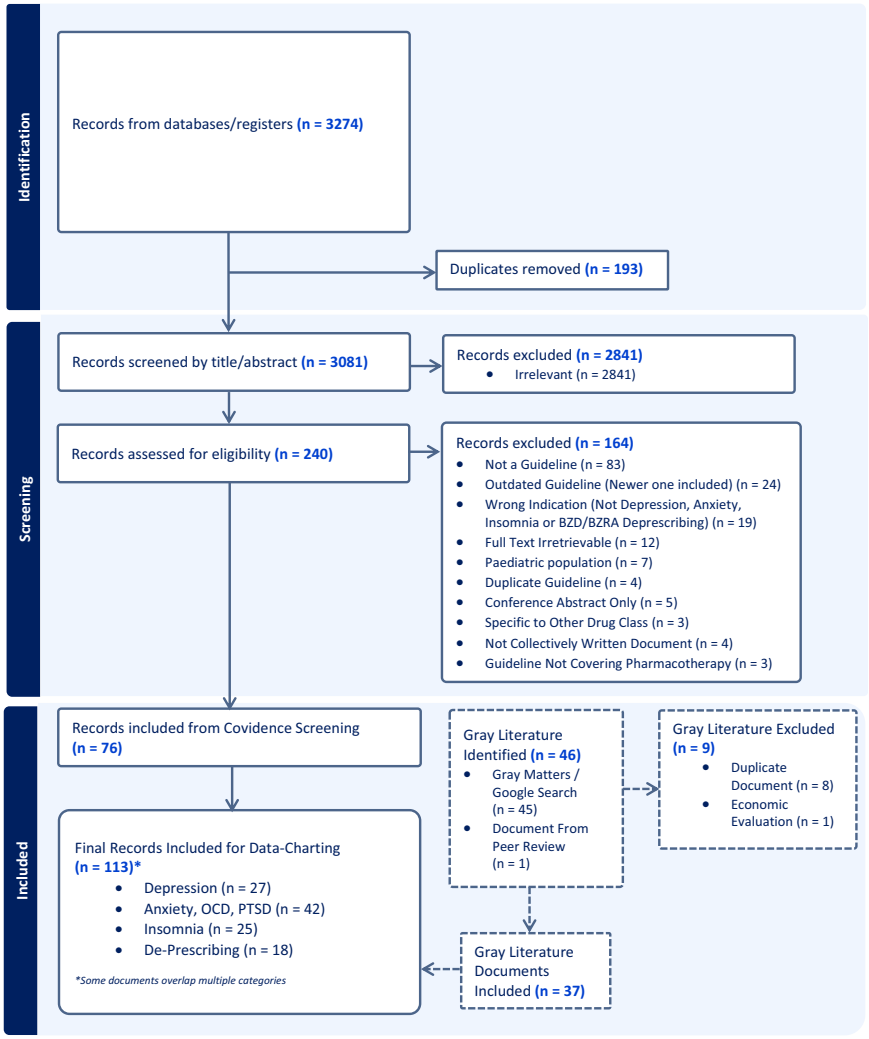

Fig. 1: PRISMA-ScR Flow Diagram Depicting Document Screening and Selection Process. Solid boxes and arrows represent the covidence biomedical literature search, screen and selection process. The dashed boxes and arrows represent the gray literature supplemental search and selection. **Abbreviations**: BZD; benzodiazepine, BZRA; benzodiazepine receptor agonist, OCD; obsessive compulsive disorder, PTSD; post traumatic stress disorder.

organizations such as the World Federation of Societies of Biological Psychiatry (WFSBP) or the World Council on Anxiety (WCA). Of 23 countries represented by this scoping review the most prominently represented were from the Western nations of Australia (n = 6), Canada (n = 12), United Kingdom (n = 7) and the United States (n = 25). Fourteen documents exclusively focused on the treatment of one or more of these conditions in a special patient population; geriatrics (n = 10), pregnancy or post-partum (n = 3) and epilepsy (n = 1). Of the final records, an additional fifteen appeared as regional or generalised standard of practice documents dedicated to BZD/BZRA prescribing standards, predominantly for both anxiety disorders (not otherwise specified) and insomnia but without specific detail to be categorised for any condition.

Prescribing of BZD/BZRA

The main results covering the particular conditions of interest, are depicted in Table 1 with a brief summary of the results for documents covering depression, anxiety disorders and insomnia to follow.

Unipolar depressive disorders

23 of 28 documents offering expert guidance on management of major depression and associated unipolar mood disorders (such as persistent depressive disorder) did not make explicit recommendations for a role of BZD in the pharmacotherapeutic treatment of these

	1st Line Pharmacologic Option	Recommended Duration of Initial Use	Preferred BZDs/BZRAs for Condition*	Direction on Prescription Issuance*
Unipolar Depressive Disorders (n = 28)[32–59]	No (n = 23) Only as Adjunct (n = 5)	Unspecified (n = 13) <4 Weeks (n = 7) 'Short-term Use' (n = 6) 4–12 Weeks (n = 2)	No/Unspecified (n = 24) Lorazepam (n = 3) Oxazepam (n = 3) Diazepam (n = 1) Temazepam (n = 1) Brotizolam (n = 1)	None (n = 24) 'prn' use preferred (n = 1) 'Lowest dose possible' (n = 2) Specific dosing provided (n = 1)
Generalized Anxiety Disorder (n = 20)[34,58,60–77]	No (n = 17) Yes (n = 3)	'Short-term Use' (n = 10) <4 Weeks (n = 7) <8 Weeks (n = 2) <12 Weeks (n = 1)	No/Unspecified (n = 9) Alprazolam (n = 8) Diazepam (n = 8) Lorazepam (n = 8) Clonazepam (n = 5) Bromazepam (n = 4) Chlordiazepoxide (n = 2) Unspecified Long-acting agent (n = 1)	None (n = 8) 'Lowest dose possible' (n = 6) 'Scheduled dosing' (as opposed to prn) (n = 4) Specific dosing provided (n = 4) 'prn' use preferred (n = 2)
Social Anxiety Disorder (n = 19)[34,58,60–65,69–72,77–84]	No (n = 17) Yes (n = 1) Only as Adjunct (n = 1)	'Short-term Use' (n = 8) <4 Weeks (n = 4) <12 Weeks (n = 2) Unspecified (n = 5)	Clonazepam (n = 9) No/Unspecified (n = 7) Alprazolam (n = 6) Bromazepam (n = 4) Lorazepam (n = 3) Diazepam (n = 1) Unspecified Long-acting agent (n = 1)	None (n = 9) 'Scheduled dosing' (as opposed to prn) (n = 4) Specific dosing provided (n = 4) 'Lowest dose possible' (n = 4) 'prn' use preferred (n = 2)
Panic Disorder (n = 19)[34,58,60–67,69–72,85–88]	No (n = 15) Yes (n = 3) Only as Adjunct (n = 1)	'Short-term Use' (n = 7) <4 Weeks (n = 6) Unspecified (n = 3) <8 Weeks (n = 1) <12 Weeks (n = 1) Permitted Long-term Use (n = 1)	Clonazepam (n = 12) Alprazolam (n = 10) Lorazepam (n = 8) No/Unspecified (n = 6) Diazepam (n = 6) Unspecified Long-acting agent (n = 1)	None (n = 6) 'Lowest dose possible' (n = 6) 'Scheduled dosing' (as opposed to prn) (n = 5) Specific dosing provided (n = 5) 'prn' use preferred (n = 2)
Obsessive-Compulsive Disorder (n = 13)[58,61,62,64,65,70,71,89–94]	No (n = 13)	<4 Weeks (n = 2) <12 Weeks (n = 1) 'Short-term Use' (n = 4) Unspecified (n = 6)	No/Unspecified (n = 11) Clonazepam (n = 2) Lorazepam (n = 2) Diazepam (n = 1) Bromazepam (n = 1) Alprazolam (n = 1)	None (n = 10) Specific dosing provided (n = 2) 'Lowest dose possible' (n = 1)
Post-Traumatic Stress Disorder (n = 12)[58,61,62,64,65,70,89,95–99]	No (n = 12)	'Short-term' Use (n = 5) Unspecified (n = 5) <4 Weeks (n = 2)	No/Unspecified (n = 10) Alprazolam (n = 2) Clonazepam (n = 2) Eszopiclone (n = 1)	None (n = 10) 'Lowest dose possible' (n = 2) Specific dosing provided (n = 1)
Insomnia (n = 25)[100–124]	Yes (n = 19) No (n = 4) Not Specified (n = 2)	<4 Weeks (n = 14) Unspecified Short-term Use (n = 3) Unspecified (n = 6) <12 Weeks (n = 2)	Zolpidem (n = 12) Zopiclone (n = 8) No/Unspecified (n = 10) Eszopiclone (n = 7) Zaleplon (n = 6) Temazepam (n = 5) Triazolam (n = 2) Other BZDs (n = 1)	None (n = 10) 'Lowest dose possible' (n = 8) Intermittent or 'prn' use preferred (n = 6) Specific dosing provided (n = 3)

*Sum numeric totals of cells in these columns may not match total documents by condition because some documents provided multiple 'preferred' drugs or directions for use.
Abbreviations: BZD; benzodiazepine, BZRA; benzodiazepine receptor agonist, prn; pro re neta (Latin–as the need arises).

Table 1: **Prescribing guidance summary by condition for benzodiazepines and benzodiazepine receptor agonists.**

conditions. The remaining 5 documents only advised their use as an adjunctive treatment to antidepressants or other modalities for short-term use.

Anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder

Of 42 documents primarily covering conditions in this category; 20 covered Generalised Anxiety Disorder (GAD), 19 covered Panic Disorder (PD), 19 covered Social Anxiety Disorder (SAD). Additionally, 13 covered Obsessive-Compulsive disorder (OCD) and 12 covered Post-Traumatic Stress Disorder (PTSD).

For all these conditions, >80% of documents in each category did not advise their use as first-line agents and most documents recommended use only when necessary for either <4 weeks or for an unspecified short-term use duration. The specific agents recommended most were diazepam and alprazolam for GAD, clonazepam and alprazolam for SAD and PD. There was significant heterogeneity in the guidance on their prescriptive use

with most guidelines or guidance documents offering either no advice, limited advice or variable guidance on their dosing or administration pattern (scheduled vs. prn use).

Insomnia

When pharmacologic use was deemed necessary for treatment, 19 of 25 documents either made explicit recommendations for BZRA or BZD as either the only 1st line treatment of choice or one of multiple 1st line pharmacologic options. The BZRA ('Z-Drugs') were clearly more often the treatment of choice over BZD. Fourteen of 25 documents advised use <4 weeks specifically. Other salient features were an emphasis on intermittent or 'prn' use (n = 6) or use of the "lowest dose possible" (n = 8).

Deprescribing

Of the total documents, 95 (84%) offered either no deprescribing recommendations (n = 69) or variably limited deprescribing recommendations insufficient for full analysis (n = 26). The remaining 18 documents covered deprescribing of BZD/BZRA in sufficient detail for data-charting (Table 2). Overall, common themes between these documents included a focus on patient shared-decision making (n = 15), gradual dose reduction (n = 18) and the possible switch to a long-acting BZD to facilitate tapering (n = 12). The documents were divided in their approach towards substitutive pharmacotherapy (i.e not a BZD) with some acknowledging this as a potential option (n = 7), others advising against this practice (n = 7) and the remainder not specifying any direction on this approach (n = 4). Only one of the documents provided commentary or guidance on unconventional tapering methods involving the alteration of solid oral dosage formulations (i.e tablet shaving, water dilution etc.) to facilitate patient guided hyperbolic dose reductions that are otherwise unavailable through standard dosage forms.

Discussion

Our results indicate a general lack of specific BZD prescription guidance in major depression and associated mood disorders other than the possible use of a BZD for less than 4 weeks adjunctively with an antidepressant. There were few guidelines that made clear recommendations for management of BZD in patients with concomitant mood and anxiety disorders.[139] Notably, BZD have been evaluated as monotherapy for depression with no observed difference from tricyclic antidepressants (TCA) in a meta-analysis of 20 trials from the 1970's to early 1990's.[140] Nevertheless, the lack of BZD treatment as a viable maintenance treatment option within guidelines for depressive disorders was not surprising for two reasons. First, BZD have been associated with worse mood outcomes long-term and may increase suicidality in vulnerable patients with other psychiatric risk-factors.[141–144] Second, there is a paucity of high-quality controlled trial evidence demonstrating benefits for adjunctive treatment with BZD beyond 4 weeks at the time of antidepressant initiation.[145]

BZD treatment specifications were provided more often in the context of perinatal/post-partum depressive disorders.[32,34,55] This could be explained by the emphasis on explicit safety considerations around medication use in pregnancy. For example, three guidelines offered explicit advice to use agents such as lorazepam, temazepam, oxazepam or brotizolam, which either undergo limited hepatic metabolism or have relatively shorter elimination half-lives to minimise theoretic fetal or lactational exposure.[32,34,55]

BZD were not recognised as first-line pharmacologic options in most documents for anxiety disorders, OCD or PTSD. Indeed, recent, high-quality, international guidelines from WFSBP only advocate use of selected BZD during the first weeks of antidepressant treatment or for treatment resistant patients without substance use disorders in PD, GAD, SAD, and somatic disorders.[77] This does not appear to represent a substantive change from past decades of clinical guidance despite past calls to re-appraise the evidence proper and place BZD on equal terms with antidepressants for first line treatment of anxiety conditions (PD in particular).[146,147]

When BZD are used for anxiety related disorders, there is a clear consensus among most documents to restrict their use to the 'short-term' (often unspecified in terms of duration) but most commonly for less than 4 weeks. Interestingly, alprazolam which has become noticeably more problematic in terms of misuse or harm based on real world data over the past two decades, is still over-represented as a BZD of choice in many guidance documents.[148] This is no doubt attributable to the larger abundance of earlier randomised controlled trial data compared to some other BZDs for conditions such as PD.[149] However, real world evidence of harm via overdose and diversion trends should be considered in framing future recommendations on BZD selection.[150–152] For instance, some newer documents specifically advise against the use of alprazolam given its rapid onset and shorter-half life; pharmacokinetic properties that increase its potential for withdrawal and misuse.[152] Other major BZD that were prominently represented were diazepam, lorazepam and, especially; clonazepam which has more long-term use data from clinical trials, particularly in PD.[153]

Another area of clear heterogeneity in guidance was in the dosing pattern recommended. Some major guidelines advise regular scheduled dosing of BZD for common anxiety disorders.[60,64,77] In contrast, other documents advise 'prn' use or intermittent dosing. How prescriptions are issued and used in real world medical practice can have profound effects on the development of tolerance or dependence for individuals with these

	Patient Demographic Emphasized for Deprescribing	Patient Engagement or Shared Decision Making Discussed	Gradual Dose Tapering	Switch to Long-Acting BZD	Non-BZD Substitutive Pharmacotherapy	Dose-Formulation Alteration Methods (i.e tablet shaving, liquid dilution, compounding)
Total (n = 18)	Long-term Use (n = 14) Older Adults (n = 7) BZD or Substance Use Disorder (n = 5) Insomnia (n = 3) Pregnancy (n = 2) PTSD (n = 1) Traumatic Brain Injury (n = 1)	Yes (n = 15) Not Specified (n = 3)	Yes—Explicitly Described (n = 13) Yes—Partially Described (n = 5)	Yes—Endorsed or Optional Depending on Circumstance (n = 12) No—Either not necessary or recommended (n = 3) Not Specified (n = 3)	No—Either not necessary or recommended (n = 7) Yes– Various agents as options for withdrawal (n = 7) Not Specified (n = 4)	Not Specified (n = 17) Yes—Described (n = 1)
Agoritsas et al. for BE-SAFE (2023)[124]	Long-term Use; Insomnia	Yes	Yes—partially described; *"When implementing strategies for deprescription of BSHs for insomnia disorder, we suggest tapering of BSHs rather than usual care."*—pg.30	Not Specified	No—*"When implementing strategies for deprescribing BSHs for insomnia disorder, we suggest NOT using pharmacologically assisted interventions (including melatonin, paroxetine, ramelteon, or dothiepin)."* Pg.42	Not Specified
Watson et al. as Alliance for Sleep (2023)[100]	Long-term Use; Insomnia	Yes	Yes—explicitly described; *"gradual dose reduction, with lowering by 10-25% increments every few days, usually over a period of 4 weeks, with the goal of discontinuing the medication."*—pg.7	No—*"No data were found to determine whether switching to a longer half-life hypnotic drug decreases withdrawal or rebound insomnia symptoms."* – pg.7	Not Specified	Not Specified
Benzodiazepine Action Workgroup of Colorado Consortium for Prescription Drug Abuse Prevention (2022)[125]	Long-term Use	Yes	Yes—explicitly described; *"Initiate with a small test reduction (≤5%). Allow the patient to lead subsequent reduction amounts/intervals based on tolerability of withdrawal symptoms."* – pg.2	Yes—*"Substitute an equivalent dose of a longer half-life BZRA (diazepam, clonazepam, chlordiazepoxide) with a stepwise crossover."* – pg.2	Yes—*"Adjunctive medication (e.g., carbamazepine, hydroxyzine) should be considered in case of severe symptoms. However, use for this indication is off-label, and there is limited evidence of benefit."* – pg.3	Yes—*describes micro-tapering methods from liquid dissolution, compounded prescription, precision scale dose reductions* – pg.3
National Institute for Health and Care Excellence & Royal College of Physicians (2022)[126]	Not Specified—*Attributable to all potential patients receiving BZD or BZRA* pg. 5-6	Yes	Yes—partially described; *specific dose tapering not included. Flexible, individualized dose reduction.*pg.19-21	Yes –*"If…withdrawing from BZD with short half-life, consider switch to a BZD with a longer half-life"*- pg.21	No—*"Do not offer sodium valproate or buspirone to aid withdrawal from a benzodiazepine"*- pg.22	Not Specified
Kaiser Permanente (2022)[127]	Long-term Use	Yes	Yes—explicitly described; *Multiple tapering regimens offered with dose reductions ranging from 25% weekly to 10% every 4 weeks* – pg.10-11	Yes—*Diazepam or Lorazepam potentially recommended with detailed instruction on how to switch* – pg.12	Yes—*Many options including carbamazepine, propranolol, valproate, gabapentin, clonidine and OTC agents depending on withdrawal* – pg.13	Not Specified
Health Services Executive—Medicines Management Program (2021)[128]	Long-term Use	Yes	Yes—explicitly described; *Dose tapering by 5-10% every 1–2 weeks with slower reduction at lower doses* – pg.32	Yes—*Diazepam conversion with gradual dose reduction described in detail* – pg.32-34	No—*beta-blockers, antidepressants and antipsychotics specifically mentioned to be avoided* – pg.33	Not Specified—*Very small dose reductions such as 500 ug of diazepam mentioned without specification of 'how' (quartering 2 mg tablets?)* – pg.33
Conn et al. (2020)[129]	Older Adults; Long-Term Use; Substance Use Disorder	Yes	Yes—explicitly described; *"Initially reducing dosage by 10–25% every one to two weeks, with slower rates of reduction later …"* pg.121	No–*Not routinely recommended. Only for certain situations such as when dosage strengths are limited or when high risk BZD such as alprazolam is used.*—pg.120	No—*"Substituting a pharmacologically different drug as a specific intervention to mitigate BZRA withdrawal symptoms during gradual dose reduction is not routinely recommended"* – pg.120	Not Specified

(Table 2 continues on next page)

	Patient Demographic Emphasized for Deprescribing	Patient Engagement or Shared Decision Making Discussed	Gradual Dose Tapering	Switch to Long-Acting BZD	Non-BZD Substitutive Pharmacotherapy	Dose-Formulation Alteration Methods (i.e tablet shaving, liquid dilution, compounding)
(Continued from previous page)						
Amanti (2018)[130]	Inpatient Older Adults in Psychiatric Unit	Yes	Yes—explicitly described; *Multiple drug specific tapering regimens offered*	Not Specified—*All tapering regimens offered did NOT switch to diazepam*	Yes—*valproate, carbamazepine, trazodone, hydroxyzine, gabapentin, pregabalin and clonidine were presented as BZD alternatives to consider*	Not Specified
Pottie et al. (2018)[107]	Older adults; Long-term use; Insomnia	Yes	Yes—explicitly described; *example regimen is 25% reduction q 2 weeks then 12.5% reduction near end of taper.*–[pg.345-346]	No—*Not routinely recommended.*–[pg.345-346]	No—*Not specified in detail. Melatonin mentioned as ineffective.*–[pg.342]	Not Specified
New Mexico Overdose Prevention & Pain Management Council (2018)[131]	Older adults; Long-term Use	Yes	Yes—explicitly described; "*25% reduction q 2–3 weeks, with if needed, a slower decrease (12.5%) for last two weeks*" [pg.6]	Yes—*Diazepam and clonazepam and extended-release alprazolam described as options for tapering*–[pg.6]	Yes—*carbamazepine, propranolol, clonidine And analgesics mentioned as potentially useful adjuncts*–[pg.4]	Not Specified
Royal Australian College of General Practitioners (2015)[132]	Older adults; Long-term Use; Pregnancy; Substance use disorder	Yes	Yes—explicitly described; *Multiple specific tapering regimens offered*-[pg.58-62]	Yes—*Diazepam conversions covered in detail* – [pg.45,62]	No—*Carbamazepine and antidepressants have limited evidence and not routinely recommended. Melatonin potentially useful.*–[pg.45]	Not specified
Haut Autorite De Sante (2015)[133]	Long-term use	Yes	Yes—partially described; *Process described but specific dose tapering not included. Gradual discontinuation individualized from 4 weeks and up to 1 year or more*–[pg.2]	Yes—*Diazepam mentioned as alternative for BZD substitution* – [pg.5]	Not Specified	Not Specified
National Center for PTSD (2015)[99]	Older adults; PTSD, Long-term Use; Substance Use Disorder; Traumatic Brain Injury	Not Specified—*Implied in terms of building a "stable relationship"* – [pg.1]	Yes—explicitly described; *specific tapering regimens offered* – [pg.2]	Yes—*Diazepam conversions covered in detail* – [pg.2]	Yes—*Mirtazapine and Carbamazepine suggested. Propranolol, Progesterone, Ondansetron, TCAs, Valproate, Trazodone, Buspirone mentioned as ineffective* – [pg.2]	Not Specified
JPS Health Network (2014)[134]	Long-term Use	Not Specified	Yes—explicitly described; *reduce by 5-10% every week in divided doses with smaller reductions monthly after 50% of original dose is reached* – [pg.6]	Yes—*Diazepam conversions covered in detail* – [pg.6]	Yes—*carbamazepine, valproate and gabapentin advised to facilitate faster taper. Buspirone, SSRI, clonidine or "sleeping aids" as adjunctive agents*—[pg.6]	Not Specified
College of Psychiatry of Ireland (2012)[135]	Substance Use Disorder involving BZD/BZRA; Pregnancy	Not Specified	Yes—explicitly described; *reduce by 1/8th of daily dose every 1–4 weeks*	Yes—*Diazepam conversions covered in detail*	Not Specified	Not Specified
Ministry of Health Singapore (2008)[136]	Older Adults; Long-term Use	Yes	Yes—Explicitly described; *dose-tapering protocols provided* – [pg.5,26-27]	Yes—*Diazepam or other long-acting agents* – [pg.26]	No—*Propanolol, dothiepin, buspirone, progesterone or hydroxyzine not recommended* – [pg.26]	Not Specified
Government of Ireland—Department of Health and Children (2002)[137]	Substance Use Disorder involving BZD/BZRA	Yes (minimal) – *Not fully emphasized. Slightly more paternalistic in deprescribing approach*	Yes—Explicitly described; *dose tapering protocols provided*–[pg.21-24]	Yes—*Diazepam conversions covered in detail* – [pg.21-24]	Yes—*potentially useful; propranolol, carbamazepine, antihistamines, or sedative antidepressants depending on withdrawal* – [pg.25]	Not Specified
Lader et al. (1993)[138]	Long-term Use	Yes	Yes—Partially described; *process described for duration between 6 weeks to 6 months but specific dose tapering not included* – [pg.1708]	Not Specified	Not Specified	Not Specified

Abbreviations: BSH; benzodiazepine and sedative hypnotics (quoted from one source) BZD; benzodiazepine, BZRA; benzodiazepine receptor agonist, OTC; over-the-counter medication, PTSD; post-traumatic stress disorder, SSRI; serotonin selective reuptake inhibitor, TCA; tri-cyclic antidepressant.

Table 2: **Deprescribing guidance for benzodiazepines and benzodiazepine receptor agonists.**

conditions and so this is an area where further clarity could be achieved within future guidelines. This is especially important because recent observational research indicates potentially safer outcomes with intermittent compared to chronic dosing.[154]

Guidance for OCD and PTSD were comparatively limited, based on lack of positive evidence of benefit, and no documents clearly advised their use as first line pharmacologic options. Furthermore, the use of BZD in PTSD has been controversial and frequently ill-advised based on their proposed propensity to interfere with fear extinction in exposure therapy as well as potentiate the development of ongoing stress symptomatology in the aftermath of a traumatic event.[155–158]

Insomnia was the only condition where these agents had a clear first line pharmacologic indication for their use. Non-pharmacological treatment approaches such as cognitive behavioural therapy (CBT-I) generally took precedence over pharmacotherapy in most of the major guidelines reviewed, and while this was not quantified in our data-charting, this has become standard knowledge among well-informed clinicians.[105,108,109] Overall, the Z-Drugs were preferable to BZD for treatment of insomnia in nearly all documents that offered significant guidance. The use of these agents, like other conditions, was typically intended for short-term use and, again, most frequently in treatment durations no longer than 4 weeks. Most likely, this is not only due to potential dependency but also because of the uncertain but possible deleterious effect of these agents on restorative sleep quality over the long-term.[159–161] Of further interest for the future of insomnia pharmacotherapy guidelines is the emergence of newer agents such as dual orexin receptor antagonists which are under-represented in older guidelines and still unavailable in some countries. These agents have shown similar early efficacy and potentially superior cognitive safety to Z-Drugs, a relevant consideration in the treatment of older adults.[162]

The focus of BZD deprescribing, especially among older adults, has become more prominent in Western and European nations especially in recent years given an aging demographic trend and the known risks of these agents in this population.[163,164] Barriers and enablers of BZD deprescribing success are being increasingly understood from the exploration of the patient and prescriber experiences.[165] Use of findings from implementation science studies, surrounding the patient-care context around BZD use, are likely to yield higher quality evidence-based deprescribing interventions to inform future guideline recommendations. Until then, our results indicate some level of both consensus and discrepancy among documents that offer significant medication-related guidance on BZD deprescribing.

In terms of general consensus, gradual dose reduction and shared decision making are universally acknowledged as foundational strategies for successful deprescribing. However, the rate of gradual dose reduction offered was inconsistent despite commonalities in prescribing principles (i.e tapering slower as doses become lower). While not explicitly examined in this review, it is nonetheless important to acknowledge that psychosocial interventions, such as cognitive-behavioural therapy, increase the success of gradual dose reduction for discontinuation of BZD/BZRA in both insomnia and anxiety disorders.[166,167]

The switch to a long-acting agent, diazepam in particular, was commonly acknowledged as an option with variation in the 'when' and 'how' of the BZD substitution approach. Some guidelines did not make this recommendation due to a scarcity of evidence.[107,129] Furthermore, accurate benzodiazepine conversion (i.e diazepam milligram equivalence) for individual patients still remain a challenge that may be improved upon by further research.[168]

Another area of contention in the prescriptive management of BZD withdrawal is the use of alternative pharmacotherapies as either adjuncts or to substitute the BZD entirely. Previous reviews have identified some agents such as carbamazepine and melatonin for their use in this setting—though results are mixed and not fully devoid of risk itself.[169,170] The documents we reviewed were quite divided in either their recommendations or even acknowledgement of these pharmacologic options as viable strategies. This is likely explained by the limited number of randomised controlled trials and lower quality heterogenous evidence variably supporting their use, as reviewed in further detail elsewhere.[163,169,170] Furthermore, the fact that there were many such agents without clear guidance on 'when' (what stage of withdrawal), 'how' (dosing and duration) and 'where' (i.e institutional or outpatient setting) to use them does not yet offer clinicians much confidence in their routine adoption as a strategy for BZD discontinuation.

A final area of interest relevant to deprescribing is the barely investigated, often patient driven, approach toward BZD formulation altering which may include tablet shaving or water dilution methods which was observed by Ashton as far back as 1994.[171] This is conceptually akin to crude hyperbolic dose reductions or 'micro' tapers, which have been previously discussed regarding antidepressant tapering.[172,173] Only one document that we reviewed descriptively covered this practice. While not clearly an acknowledged evidence-based strategy yet, future guidelines and guidance committees on BZD and BZRA medication would do well to acknowledge the reality of this practice and make recommendations on it regardless of the state of evidence. Pharmaceutical compounding as a routine alternative to problematic protracted low-dose withdrawal situations may be expected to yield a more standardised, clinician supervised and ultimately successful approach for refractory patients, but could be cost-limiting or inaccessible for many of these individuals.

There are some important limitations to this review. Despite a comprehensive search strategy, there are potentially guidance documents or guidelines that may have been missed and so we cannot claim completeness. For instance, there was a preponderance of records from North America and Europe which may limit relevance or generalisability of our findings for other parts of the world. However, given the abundance of documents reviewed and the general consistency between them, we doubt that this would dramatically impact our general findings. Of high importance is the possibility of occasional error in the human interpretation and data-charting of >2000 data elements (113 records x 19 variables each) in Covidence and the transfer of this data to Excel for transparent availability to readers. Despite that data-charting was double-checked for confirmation with methodology adhered to, it is no guarantee against occasional human data-entry error. Artificial Intelligence tools, increasingly used in the conduct of literature reviews may offer a precision update of this type of work in the future.[174]

Few major BZD "guidance" documents that have garnered a well-earned international reputation, such as the Ashton manual, were not included due to either their nature as single-authored documents or explicit statements therein that the information contained is for use by the general public as opposed to healthcare providers (the Ashton manual fulfills both) working with patients.[175] General medication use guidelines such as STOPP-START or the Beers criteria in geriatrics were also not used due to their lack of specificity on BZD/BZRA use.[176,177] Other existing guidelines such as those for acute agitation, psychosis, bi-polar mania or behavioural-psychological symptoms of dementia, that may have offered guidance on BZD/BZRA use, did not fall within the scope of our review. Lastly, there was no quality appraisal of the guidelines or guidance documents conducted. However, our goal was not to determine which guideline should be held as the most authoritative but rather to attempt a comprehensive summary of international expert opinion on the use of BZD and BZRA for common psychiatric conditions.

Over thirty years of prescriptive guidance on BZD and BZRA, from groups of international clinician experts on anxiety disorders, unipolar depressive disorders, and insomnia, demonstrate that these agents are still clearly not recommended as routine 1st line agents or for longer-term use (i.e beyond 4 weeks) in most patients. Recommendations on their use have not generally changed but the lack of explicit direction on prescribing details, noted in many documents, can be further elaborated on in future iterations of guidelines.

A renewed focus on deprescribing of these agents within the past 10-years has elucidated areas of attention for research work to inform future guideline development panels. The shifting of deprescribing practices involving BZD from a clinical 'art' to a clinical 'science' based practice should be a continued focus for guideline committees, with attention to comparing dose reduction strategies, the use or non-use of diazepam (or other long-acting BZD), the use or non-use of adjunctive pharmacotherapies and the value of 'micro' tapers using either compounded products or patient directed alteration of available dosage forms.

Contributors

JB, JB, ML, DN had full access to all the data in the study and take responsibility for the integrity and the accuracy of the data analysis. Study concept and design: JB (Brandt), SW Acquisition of data: JB (Brandt), ML. Administrative and technical support: ML. Screening and Data-Charting: JB, JB, DN. Analysis and interpretation of data: JB, JB, DN Results Validation: JB (Bressi), JWD, MWD, CC, SW Drafting of the original manuscript: JB (Brandt) Critical revision and review of the manuscript for important intellectual content: JB, JB, ML, DN, CC, JWD, MWD, SW. Project supervision and guarantor: JB (Brandt). All authors read and approved the final manuscript.

Data sharing statement

Final data analysed from this study is available on Mendeley Data downloadable as an excel-file and embargoed for publication on 12/04/2024 at https://doi.org/10.17632/sb2r9v2635.1. Supplemental appendices including study protocol, sample search strategies and PRISMA checklists are available within the supplemental appendix. Lastly, access to the archived covidence review and associated bibliographic data can be facilitated by contacting the corresponding author subject to review by the Neil John Maclean, Health Sciences Library at the University of Manitoba.

Ethics statement

This study used only published information from existing and publicly available documents. There were no human participants in this research. The requirement for ethical approval and informed consent was waived for this study.

Role of the funding source

There was no funding source for this study. All authors were granted access to the underlying data and accept responsibility for the decision to submit for publication.

Declaration of interests

Brandt, Bressi, Cadogan, Witt-Doerring (M & J) and Wright have all served as either advisors or directors to the Alliance for Benzodiazepine Best Practices; a not-for-profit organization with the mission to inform evidence-based improvements in the use of benzodiazepines and Z-drugs. Wright has received personal payment (unrelated to this project) for his past service as medical director of the Alliance for Benzodiazepine Best Practices.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102507.

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