PROPOSAL TO REVISE THE INDICATIONS FOR THE USE OF BENZODIAZEPINE MEDICINES IN THE TREATMENT OF ADULTS WITH ANXIETY DISORDERS

WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation

University of Verona, Verona, Italy

Persons to contact:

Davide Papola, MD, PhD: davide.papola@univr.it

Corrado Barbui, MD: corrado.barbui@univr.it

Contributors:

Dr. Davide Papola; WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona

Dr. Chiara Gastaldon; WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona

Dr. Giovanni Ostuzzi; WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona

Prof. Corrado Barbui; WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona

None of the contributors have conflicts of interests to declare.

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1. **Summary statement of the proposal to revise the indications for the use of benzodiazepine medicines in the treatment of adults with anxiety**

In this application, we propose to revise the indications for the use of benzodiazepine (BDZ) medicines in the World Health Organization (WHO) Essential Medicines List (EML), section 24.3 "Medicines for mental and behavioural disorders >> Medicines for anxiety disorders" by:

1	Adding an asterisk to diazepam with the following statement: * "For the short-term emergency management of acute and severe anxiety symptoms only";
2	Adding the following medicines as therapeutic alternatives (restricted square box (□)): lorazepam

With reference to the first point, our proposal is based on the following considerations:

a) BDZs are rapidly effective rescue treatments for anxiety manifestations when symptoms are severe, disabling or causing extreme distress. The benefit-risk ratio of using BDZs may be favorable for short-term periods.

b) On the other hand, the prolonged use of BDZs may expose to risks of abuse, misuse, and addiction.

c) The continued use of BDZs may lead to clinically significant tolerance and physical dependence. The risks of dependence increase with longer treatment duration and higher daily doses.[1]

d) Abrupt discontinuation or rapid dosage reduction of BDZs after continued use may precipitate acute withdrawal reactions, which can be life-threatening.[2]

e) Long-term use of BDZ can lead to numerous adverse effects, especially in older individuals.[3,4]

f) There is unanimous consensus among guidelines to limit BDZ prescriptions to short-term periods only (see below paragraph 7, "Treatment details").

g) The Guidelines Development Group of WHO Mental Health Gap Action Programme (mhGAP) revision is considering recommending that:

"*Benzodiazepines should not be used for the treatment of adults with generalized anxiety and/or panic disorder. For emergency management of acute and severe anxiety symptoms, benzodiazepines may be considered but only as a short-term (7 days maximum) measure."*

It is expected that these two recommendations will be approved by the WHO Guidelines Review Committee by the time of the next meeting of the Expert Committee on EML.

Point two is justified by the indication of WHO to specify alternative treatment options for square box-tagged medicines. We propose to add lorazepam, as an alternative to diazepam, because:

a) BDZ medicines are a vast and heterogeneous group of medicines. More than 1000 BDZs have been synthesized so far.[1] At the moment there are between 35 and 40 available on the market, globally (appendix 1 and 2). In its current version, through an unrestricted square box, the EML is recommending any BZD to be equivalent to diazepam for the treatment of anxiety disorders. Such a

recommendation was probably formulated considering that BDZs have all similar efficacy and tolerability profiles, yet variations in the duration of action, potency, and risk of addiction of the different BDZs do exist and should be taken into due consideration.

b) Diazepam is a medium potency BDZ with a long half-life (up to 80 h); lorazepam is a high-potency BDZ with a short half-life (up to 20 hours) which is prescribed for the short-term management of anxiety and insomnia. Both are globally available and cheap medicines that can be prescribed by non-specialist physicians.

c) Although all BDZs carry an intrinsic potential for abuse, misuse, and dependence, there are some that have been clearly identified by authorities as carrying specific risks for addictive behaviors (for e.g., alprazolam, flunitrazepam, temazepam). Currently, there is potential to misinterpret WHO's EML as stating all BDZs as essential. Our application to limit these BDZ to diazepam and lorazepam eliminates this misinterpretation.

d) Diazepam and lorazepam are the two BDZs with the widest labelling indications.[5]

2. Consultation with WHO technical departments

Dr. Mark van Ommeren; WHO Department of Mental Health & Substance Use

Dr. Brandon Gray; WHO Department of Mental Health & Substance Use

3. Other organization(s) consulted and/or supporting the submission.

Dr. Biksegn Asrat was consulted as an expert in the field of Public Mental Health and psychopharmacology. Dr Asrat works at the Department of Psychiatry, University of Gondar, Ethiopia.

4. Key information for the proposed medicines.

Table 1. ATC code, dosage forms, pharmacokinetic features, and therapeutic indications of interest for this proposal

name	ATC Code	Dosage forms and strengths	Pharmacokinetic	Medicine half-life	FDA indication
diazepam	N05BA01	Tablet: 2, 5, 10 mg Liquid	Well-absorbed orally; bioavailability 90%; time to peak concentration 0.5-6 hours (rapid); 95-98% protein binding; Distribution: 1 L/kg; Metabolized by the liver (CYP2C19 and CYP3A4: glucuronidation, methylation, oxidation, and hydroxylation) and excreted primary by kidneys	20-80	Anxiety disorders
lorazepam	N05BA56	Tablet, sublingual tablet: 0.5, 1, 2 mg Liquid	Well-absorbed orally; bioavailability 90%; time to peak concentration 1-2 hours (intermediate); 85-91% protein binding; Distribution: 1.3 L/kg; Metabolized by the liver (glucuronidation). Excreted primary by kidneys and some via feces	10-20	Anxiety disorders

FDA: Food and Drug Administration; ATC: Anatomical Therapeutic Chemical Classification (https://www.who.int/tools/atc-ddd-toolkit)

5. Proposal for an individual medicine or representative of a pharmacological class / therapeutic group.

We are proposing to specify that lorazepam should be considered in a "selected" square box in addition to oral diazepam in the section 24.3 "Medicines for mental and behavioral disorders >> Medicines used in anxiety disorders".

6. Information supporting the public health relevance.

People suffering from anxiety disorders usually experience excessive fear, nervousness, worry and avoidance of potential or perceived threats in the environment,[6] and are often burdened by autonomic dysfunction, such as palpitations, dizziness and insomnia.[7] Anxiety disorders are receiving more and more attention, due to their high incidence, early age of onset, and tendency to relapse for a long time and for their disabling nature.[8] Anxiety disorders are major drivers of the global burden of disease, as measured in prevalence, disability-adjusted life-years, and years lived with disability.[9]

Although guidelines clearly indicate selective serotonin reuptake inhibitors (SSRIs) as the first-choice pharmacological treatment for anxiety disorders,[10-14] recommendations are not fully implemented in clinical practice.[1] Many clinicians still regard BDZs as acceptable treatment options, both in the acute and chronic phase of the treatment of anxiety disorders, partially because of their rapid onset of action and favorable side effect profile in the short-term, and also because therapeutic response and side-effects of alternative medicines are not always fully satisfying.[1,15]

At the same time, BDZs are all classified under the WHO Convention of Psychotropic Substances as Schedule IV (except for flunitrazepam and temazepam, which are scheduled as III because of perceptions of greater dangers), and therefore they are a "substance of abuse".[16]

It has been estimated that in 2020 4.8 million individuals misused or abused prescription BDZs in the United States (US),[17] which have a high addictive potential compared to other psychotropic medicine. For example, a population-based cohort study used a nationwide cohort of almost 130 000 new BDZs users in Finland found that 39.4% (51 099) of the continuous BDZ users became long-term users (long term used defined as continuous BDZ use of at least 180 days).[18]

Long-term use of BDZ can lead to numerous adverse effects, especially in older individuals.[3,4] Specifically, among older persons, BDZ long-term use has been associated with cognitive and psychomotor adverse effects and an increased risk of falls,[19] fractures,[20,21] and even mortality among many age ranges.[22,23] General factors associated with long-term BDZ use include sex, comorbid conditions, older age, lower income/receipt of social benefits, psychiatric comorbidities, substance abuse and poorer health status.[18,24-26]

Concerns about the noxious long-term effects of BDZs have widely permeated society through mass media campaigns and safety advocates stakeholder oganizations.[27-29] Institutions have been collaborating with stakeholders to identify what positive action can be taken to support patients with regard to prevention, identification and management of long-term side effects of BDZs.[30]

There has been also concern for more than 50 years regarding BDZ development of tolerance and physical dependence.[31,32] The dependence issue is becoming increasingly worrying, as it can occur when BDZs are taken steadily even for several days or weeks.[1] Patients who became physically dependent can have withdrawal signs and symptoms when the medicine is tapered or continued in lower doses,[1] with tapering requiring months to years for most individuals and with the majority of users failing to achieve sustained discontinuation.[33,34] Indeed, population-based studies have found only 13% of adults who take benzodiazepines long-term (more than 4 months) have been able to discontinue use within 1 years' time.[35] What's more, BDZs often lead to re-initiation of use even after discontinuation in the majority of users, with an estimated two in three people who have tapered off long-term benzodiazepine treatment resuming use sometime thereafter.[36] Also, stopping BDZs abruptly or reducing the dosage too quickly can result in acute withdrawal reactions, including seizures, which can be life-threatening.[2]

Furthermore, reports both in Europe and in US consistently highlight that concomitant use of BDZs and opiates is a major risk factor in drug-related deaths.[37,38] Notably, evidence shows that, excluding alcohol, BDZs are along with cannabis the psychoactive substances most prevalent in the driving population. BDZ use may cause drowsiness, impair judgement and increase reaction time, and so affect ability to drive or perform skilled tasks.[5] When alcohol is also used, the risk of being involved in or responsible for a road accident is significantly increased.[39]

In September 2020, the U.S. Food and Drug Administration (FDA) announced an update to the Boxed Warning, the agency's most prominent safety warning, and required class-wide labeling changes for all BDZs to include the risks of abuse, misuse, addiction, physical dependence and withdrawal reactions to help improve their safe use.[40] Many of the document's conclusions raise the same concerns BDZ safety advocates have had for decades.[41,42]

7. Treatment details

BDZs are a group of central nervous system depressants exerting different clinical effects at different dosages. As their dosage increases, all BDZs produce anxiolytic, hypnotic, myorelaxant, anticonvulsant, and anesthetics effects, respectively. BDZs all bind to specific sites on the γ-aminobutyric acid (GABA) type A ($GABA_A$) receptor, increasing the receptor's affinity for GABA, an inhibitory neurotransmitter. Specifically, the activation of the $GABA_A$ receptor triggered by BDZs causes a conformational change to the GABA's receptor central pore, which allows the entrance of chloride ions into the neuron. The influx of the chloride anion hyperpolarizes the neuron, resulting in the decreased firing of action potentials of that neuron.

The main sites of action of the BZDs are in the spinal cord, where they mediate muscle relaxation, in the brain stem, causing numbness, and in the limbic and cortical areas involved in emotional experience and behaviour.[43] As a clinical consequence, anxiolysis, drowsiness and sleep are induced by BDZs taken at low dosages. Such a comforting and fast-acting feeling of calm, together with the fact that BDZs are generally cheap and widely available on the market, made BDZs the highest-selling medicines for decades in western countries.[44]

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), there are 35 BDZ derivatives under international control at the moment (appendix 1). Conversely, the WHO Anatomical Therapeutic Chemical (ATC) Classification lists 15 and 25 BDZ compounds as "hypnotic" or "anxiolytic" agents, respectively (appendix 2). Nevertheless, there is no clear division from a clinical point of view, as most BDZs classified as anxiolytics will induce sleep if taken at night and most BDZs classified as hypnotics will sedate when taken during the day. A more pragmatic method to classify the different BDZ medicines is according to their half-lives (i.e., the hours it takes for the amount of a drug's active substance to reduce by half by body's metabolism processes). Generally, BDZs are classified as having long, intermediate, and short (sometimes also "ultra-short") half-lives, although there is no definite consensus on their definition, and different interpretations have been suggested.[45-48] To complicate matters, half-lives vary between individuals.

The first BDZ to be approved and introduced in clinical practice was chlordiazepoxide (Librium), which was synthesized by the Hoffmann-LaRoche laboratories and marketed in 1960. Diazepam (Valium) was the second BDZ ever to be released in 1963, by Hoffmann-La Roche. For most years until its patents ran out in 1985, diazepam was the highest-selling drug in the United States. Lorazepam (Ativan, Tavor) was approved by FDA on September 30, 1977, for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms.

Diazepam and lorazepam are the two BDZs with the widest range of clinical indications, being approved to treat generalized anxiety disorder, insomnia, seizures, social phobia, and panic disorder, but are also indicated for premedication before some medical procedures.

Guidelines and recommendations for BDZ prescribing clearly indicate that duration of use should be limited to the short-term, and at the lowest possible dose to reduce the risks of tolerance, dependence, and withdrawal symptoms (table 2).

Table 2. Excerpts from national and international guidelines on the pharmacological treatment of anxiety disorders

Source	Year	Excerpts from the guideline
The National Institute for Health and Care Excellence (NICE)[14,49]	2013	▪ Do not offer a benzodiazepine for the treatment of generalized anxiety disorder in primary or secondary care except as a short-term measure during crises. Follow the advice in the BNF on the use of a benzodiazepine in this context. ▪ Benzodiazepines should not be used as an ongoing treatment for alcohol dependence. ▪ Benzodiazepines are associated with a less good outcome in the long term and should not be prescribed for the treatment of individuals with panic disorder.
British National Formulary[5]	2020	▪ Avoid prolonged use (and abrupt withdrawal thereafter).
British Association of Psychopharmacology (BAP)[50]	2013	▪ To reduce the risk of dependence on benzodiazepines they should generally not be prescribed as a regularly administered medication for longer than four weeks. Ideally, they should be given on an 'as required' basis and intermittently every few days during this period. ▪ Even after short-term use, a tapering-off regime (i.e., at least two weeks at reduced dosage) should be considered to minimize the risk of rebound phenomena, that is, the reappearance of symptoms present prior to treatment.
American Psychiatric Association[51]	2009	▪ The benefit of more rapid response to benzodiazepines must be balanced against the possibilities of troublesome side effects (e.g., sedation) and physiological dependence that may lead to difficulty discontinuing the medication.
European guideline for the diagnosis and treatment of insomnia[52]	2017	▪ BDZs are effective in the short-term treatment of insomnia (≤4 weeks; high-quality evidence). ▪ Long-term treatment of insomnia with BDZs is not generally recommended because of a lack of evidence and possible side-effects/risks (strong recommendation, low-quality evidence).
The German guidelines for the treatment of anxiety disorders[53]	2015	▪ The guideline group advised against the use of benzodiazepines because of their abuse potential. However, in exceptional cases (e.g., severe cardiac disease, contraindications for the standard drugs, suicidality, and other conditions), benzodiazepines can be used for a limited time period after their risks and benefits have been weighed carefully.
The Royal Australian and New Zealand College of Psychiatrists (RANZCP)[54]	2018	▪ In general, benzodiazepine use should be restricted to short term periods only. Longer term use should only be considered in patients who do not respond to adequate trials of other evidence-based pharmacological and psychological treatments. ▪ Patients should be advised that benzodiazepines may produce both tolerance and dependence, with the risk of withdrawal symptoms. Patients should also be informed of the full range of possible side effects, including cognitive impairment.

		▪ The dosage used should be the lowest effective dose necessary to achieve symptomatic relief. Prescribers should be aware of the risk of dose escalation in long term use and ensure this does not happen.
Canadian Anxiety Disorders Guidelines Initiative[12]	2014	▪ benzodiazepines are second-line options, they may be useful for the short-term management of acute or severe agitation or anxiety.
WHO Mental Health Gap Action Programme (mhGAP)	2023	The Guideline Development Group of WHO Mental Health Gap Action Programme (mhGAP) revision is considering recommending that: • "Benzodiazepines should not be used for the treatment of adults with generalized anxiety and/or panic disorder. For emergency management of acute and severe anxiety symptoms, benzodiazepines may be considered but only as a short-term (3-7 days maximum) measure. It is expected that these recommendations will have been approved by the WHO Guidelines Review Committee by the time of the next meeting of the Expert Committee on EML.

For decades BDZs have been recommended as the standard treatment of anxiety.[55,56] During the late 1990s, clinical recommendations for first line treatment of anxiety disorders changed to SSRIs. Despite these recommendations, literature shows that long-term use of BDZs is still very common to treat anxiety, even though cognitive behavioural therapy (CBT) and/or antidepressants are first-line therapy for anxiety disorders based on the evidence.[57-59]

This is a major point to prompt the WHO to make it clear that BPZs shall be used for the emergency management of acute and severe anxiety symptoms only, and for short periods only. While BDZ medicines can still play a major role in the acute management of severe anxiety surges, their use must be limited to the short-term, for safety reasons.

8. Review of benefits: summary of evidence of comparative effectiveness

The greatest advantage of BDZs is their quick onset of action.[47] As demonstration of some improvement often takes 4–6 weeks with SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs), BDZs may be useful for patients with very distressing or impairing anxiety symptoms in whom rapid symptom control is critical. Consequently, BDZs may be used along with antidepressants to help control symptoms until the antidepressant takes effect, followed by slow tapering of the BDZ.

There is unanimous consensus upon the fact that BDZs are all similarly effective against placebo, and that no BDZ is more or less effective as compared to another BDZ.[60] Based on such a premise, the numerous meta-analyses that investigated on the efficacy of BDZs always considered BDZs as a group to be confronted with other medicines or classes of medicines. For example, two meta-analyses compared the effectiveness of psychological and pharmacological treatments,[61] and the effect of antidepressants and BDZs compared with placebo.[62] Both reviews showed superiority of BDZs to placebo in the treatment of panic disorder in adults (comparative efficacy between different BDZs was not investigated at the trial level). Such results were confirmed by a recent and methodologically sound Cochrane review, which estimated a risk ratio (RR) for response to treatment to be 1.65 [95% confidence interval (CI) 1.39 to 1.96; number needed to treat (NNT) 4] in favor of BDZs.[63] Also, the dropout rate was lower among participants treated with BDZs (RR 0.50, 95% CI 0.39 to 0.64; NNT 6). Similar results were also found for generalized anxiety disorder,[64] social anxiety disorder,[65,66] and specific phobias.[67,68] Of note, the validity of the aforementioned randomized and meta-analytic findings may be hampered by detection and attrition bias, and probable publication bias. Most importantly, the included studies were only short-term studies and did not examine the long-term efficacy nor the risks of dependency and withdrawal symptoms.

A recent network meta-analysis that investigated on the efficacy of medicines to treat insomnia analyzed the comparative efficacy of BDZs, grouping them according to their half-lives (short-acting, intermediate-acting, and long-acting).[69] No differences in the acute treatment of insomnia were found between the three groups of BDZs, with standardized mean differences ranging from 0.36 and 0.83. Although indirectly (the outcome was resolution of insomnia instead of efficacy on anxiety symptoms) this finding reinforces the evidence that, when administered at the same equivalent dosage (Table 3), BDZs are all expected to exert the same beneficial effect on symptoms.

Based on these considerations, the present proposal does not suggest lorazepam as an alternative to diazepam because lorazepam is more effective than other BDZs. We suggest adding lorazepam firstly because it represents a perfect fit to complement diazepam from a pharmacokinetic point of view, as diazepam has a long half-life (20-80 h), while lorazepam has a short half-life (10-20 hours).[45] Further, diazepam and lorazepam are a good match for their therapeutic indications, as diazepam is a medium potency BDZ - indicated to treat milder forms of anxiety, while lorazepam is a high-potency BDZ - exerting robust actions against the surges of anxiety during panic attacks.[45] Lorazepam is also commonly prescribed for the short-

term management of insomnia, and thanks to its short half-life it does not cause hang-over symptoms on the next morning or day, as it might be the case with long-acting BDZ hypnotics (e.g. diazepam, flurazepam). Lorazepam also does not cause early rebound symptoms that might occur with ultra-short half-lived BDZs (e.g., triazolam), thus it can be considered as a very well-balanced compound from a pharmacokinetic perspective. There have been calls to try to avoid the use of fast-acting, short half-life BDZs such as lorazepam, because the slower onset and longer acting BDZs like diazepam or clonazepam would be less likely to be abused, less habit-forming, and easier to discontinue.[70] While this is anecdotal reasoning, and adequate comparative trials are lacking, diazepam is already in the EML representing long acting BDZs. We think that adding just one BDZ (lorazepam) to eliminate all the others through the selected square box could be an added value to the EML. Although all BDZs carry an intrinsic potential for abuse, misuse, and dependence, there are some that have been clearly identified by authorities as carrying specific risks for addictive behaviors, for e.g., alprazolam, flunitrazepam, temazepam (table 3, section 9). Currently, there is potential to misinterpret WHO's EML as stating all BDZs as essential. Our application to limit these BDZ to diazepam and lorazepam eliminates the potential for such a misinterpretation.

Both diazepam and lorazepam have widely labelled indications, are globally available, and are cheap medicines that can be prescribed by non-specialist physicians. For their complementary pharmacokinetic profiles, widespread global availability, and accessible costs, we claim diazepam and lorazepam can be representative for the entire class of BDZs in the EML section 24.3 "Medicines for mental and behavioral disorders >> Medicines used in anxiety disorders".

Table 3. Selected BDZs ordered according to their potency (adapted from Chouinard 2004)[45]

Potency/benzodiazepine/ Therapeutic indications	Approximately Equivalent Oral Doses, mg	Half-life, hours	Indications (FDA, British National Formulary)	Notes	Eligible for inclusion in the WHO EML?
Low - Very mild generalized anxiety or insomnia					
Chlordiazepoxide	10	7-30	- Short-term use in anxiety - Treatment of alcohol withdrawal in moderate dependence - Treatment of alcohol withdrawal in severe dependence	Wrong indication, availability issues	No
Oxazepam	15	6-24	- Anxiety (short-term use) - Insomnia associated with anxiety	Wrong indication, availability issues	No
Temazepam	30	8-24	- Insomnia (short-term use) - Conscious sedation for dental procedures - Premedication before surgery or investigatory procedures	Safety concerns (see section 9)	No
Medium - Mild generalized anxiety disorder					
Clorazepate	7.5	30-60	- Anxiety disorders	Diazepam is already present for the medium potency BDZ category	No
Diazepam	5	20-80	- Muscle spasm of varied aetiology - Acute muscle spasm - Tetanus - Muscle spasm in cerebral spasticity or in postoperative skeletal muscle spasm - Anxiety - Insomnia associated with anxiety - Severe acute anxiety | Control of acute panic attacks | Acute alcohol withdrawal - Acute drug-induced dystonic reactions - Acute anxiety and agitation - Premedication/ Conscious sedation for procedures, and in conjunction with local anaesthesia - Status epilepticus | Febrile convulsions | Convulsions due to poisoning - Life-threatening acute drug-induced dystonic reactions - Dyspnoea associated with anxiety in palliative care - Pain of muscle spasm in palliative care	Already present in the EML	Yes

Estazolam	-	10-24		Diazepam is already present for the medium potency BDZ category	No
Flurazepam	-	72	- Insomnia (short-term use)	Diazepam is already present for the medium potency BDZ category	No
Prazepam	30	30-60		Diazepam is already present for the medium potency BDZ category	No
Quazepam	-	15-35		Diazepam is already present for the medium potency BDZ category	No
High - Panic attacks, generalized anxiety disorder, insomnia, agitation, mania					
Alprazolam	0.5	6-20	- Short-term use in anxiety	Safety concerns (see section 9)	No
Bromazepam	3	8-19		Availability issues	No
Clonazepam	0.25	5-30		Excessive potency	No
Lorazepam	1	10-20	- Short-term use in anxiety - Short-term use in insomnia associated with anxiety - Acute panic attacks - Conscious sedation for procedures - Premedication - Status epilepticus, Febrile convulsions, Convulsions caused by poisoning		Yes
Flunitrazepam	0.5	16-35		Safety concerns (see section 9)	No
Triazolam	0.25	2-5	- insomnia	Wrong indication, ultra-rapid half-life	No

9. Review of harms and toxicity: summary of evidence of comparative safety

Consistently with what is reported for efficacy (section 8), BDZ medicines share similar tolerability profiles and, with some exceptions (table 3), abuse misuse and dependence potential.

Side effects of BDZs, withdrawal symptoms, and drug-drug interactions for diazepam and lorazepam are reported in table 4, 5, and 6 respectively. Safety considerations in special populations for diazepam and lorazepam are reported in box 1.

Table 4. Side effects of BDZs

Short-term	Long-term	Overdose
• drowsiness • confusion • dizziness • feeling sleepy • feeling tired or weak • muscle weakness • memory impairment • impaired coordination • psychomotor retardation • increased anxiety or disinhibition (paradoxical reaction, especially in elderly patients) • delirium (especially in elderly patients)	• cognitive impairment • increasing the risk of falls (hip fracture) • increasing the risk of vehicle accidents • depression and emotional blunting (in extreme cases emergence of suicidal ideation)	• extreme sedation or drowsiness • low breathing rate • confusion and difficulty thinking • slurred speech • loss of muscle control • coma It can be fatal if: • uses the drugs with alcohol or opioids

Dependence on BDZs is more common in populations which already are substance-abusing. It has been found that 11 to 15 percent of the adult population has taken a BDZ one or more times during the preceding year, but only 1 to 2 percent have taken BDZs daily for 12 months or longer.[71] In psychiatric treatment settings and in substance-abuse populations though, the prevalence of BDZ use, abuse and dependence is substantially higher than that in the general population.[72,73]

The development of physical dependence is somewhat predictable and is proportional to the total BDZ exposure (dose × duration of treatment), but since it is known that incidence of BDZ overdose mirrors BDZs availability[74,75] it is tautologic that the most available BDZs are also the most abused. At the same time though, the most available BDZs are also the most accessible and easy to buy-and-stock by governments of low- and middle-income countries, making them suitable for recommendation in the EML. This may be another reason why lorazepam should be added to diazepam in the EML. Diazepam and lorazepam are not more dangerous than other BDZs when it comes to weighing BDZ's addictive potential. There are indeed BDZs which are more dangerous than others in terms of addictive potential. For example, flunitrazepam is illegal in the US,[76] temazepam is banned in Sweden,[1] and alprazolam was scheduled among drugs that causes dependence in Australia.[77]

As a result of physical dependence, withdrawal symptoms emerge with rapid dose reduction or abrupt discontinuation of the drug. Withdrawal symptoms are possible after only one month of daily use (Table 4).[78]

Table 5. Possible withdrawal symptoms after abrupt BDZ discontinuation

Short-term withdrawal symptoms	Possible protracted withdrawal symptoms
• anxiety and panic • agitation and restlessness • tremors • dizziness • fatigue • sleep problems • shortness of breath • sweating • flushing • muscle cramps • seizures • hallucinations • gastrointestinal problems • feelings of unreality • headaches and muscle pain	Prolonged (for several months) anxiety, depression and insomnia. Physical symptoms related to gastrointestinal, neurologic, and musculoskeletal effects may occur.

Table 6. Drug-drug Interactions for diazepam and lorazepam (from "The Johns Hopkins Psychiatry Guide")[46]

Drug	Effect of Interaction	Recommendations/Comments
Diazepam – digoxin (Lanoxin)	Increased levels of digoxin	Monitor levels of digoxin, and reduce dose as needed
Diazepam – disulfiram (Antabuse)	Increased levels of diazepam	Adjust dose of diazepam as needed, or change to a benzodiazepine eliminated by glucuronidation
Diazepam – etravirine (Intelence)	Increased levels of diazepam	Adjust dose of diazepam as needed
Diazepam - fluvoxamine (Luvox)	Increased levels of diazepam	Adjust dose of diazepam as needed, or change to a benzodiazepine eliminated by glucuronidation
Diazepam – Fosamprenavir (Lexiva)	Increased levels of benzodiazepine	Adjust dose of benzodiazepine as needed
Diazepam - itraconazole (Sporanox)	Increased levels of diazepam	Adjust dose of diazepam as needed
Diazepam, lorazepam – olanzapine (Zyprexa)	Increased risk of cardiorespiratory depression	Avoid use of parenteral benzodiazepines and IM olanzapine
Diazepam – phenyton (Dilantin), fosphenytoin (Cerebyx)	Reduced levels of phenytoin	Monitor phenytoin levels, and adjust dose as needed
Lorazepam - probenecid	Increased levels of lorazepam	Reduce lorazepam starting dose by 50%; adjust dose further as needed
Diazepam – ritonavir (Norvir)	Increased levels of benzodiazepine	Adjust dose of benzodiazepine as needed
Diazepam – saquinavir (Invirase)	Increased levels of benzodiazepine	Adjust dose of benzodiazepine as needed
Lorazepam – valproate (Depakote)	Increased levels of lorazepam	Reduce lorazepam starting dose by 50%; adjust dose further as needed

Box 1. Safety consideration in special populations for diazepam and lorazepam[46,79]

Geriatric
Elderly patients often require lower BDZ doses due to slower metabolism of the drugs. They are thus more at risk from the side-effects which include drowsiness, ataxia (staggering gait), mental confusion, impaired judgement and anterograde amnesia.

Diazepam: Use 2 mg daily initially and increase as needed/tolerated.

Lorazepam: Use an initial dose of 1 mg/day in divided doses and increase as needed/tolerated.

Renal

Diazepam: No dose adjustment is needed; increase as needed/tolerated. Diazepam might increase cerebral sensitivity in renal impairment which may result in excessive sedation and encephalopathy.

Lorazepam: No dose adjustment is needed; increase as needed/tolerated. Patients with impaired renal function should be monitored frequently and have their dosage adjusted carefully according to response. Lorazepam as an intact drug is not removed by dialysis. The glucuronide metabolite is highly dialysable but is pharmacologically inactive. Increased CNS sensitivity in patients with renal impairment.

Hepatic

Diazepam: Reduce the usual dose by 50%.

Lorazepam: No dose adjustment is needed; increase as needed/tolerated. Patients with impaired renal function should be monitored frequently and have their dosage adjusted carefully according to response.

Pregnancy

BDZs cross the placenta and are classified as class D teratogens. They may lead to the development of dependence and consequent withdrawal symptoms in the fetus.[47,80] BDZs are excreted in breast milk and thus are usually contraindicated in breast-feeding mothers.[47]

10. Summary of available data on comparative cost and cost-effectiveness.

10.1 Comparative cost data amongst BDZs

The availability and affordability of BDZs varies widely across countries and according to sector (public versus private), as well as supplier (originator versus generic) prices. BDZs are routinely available in different countries at a range of prices. The "Management Science for Health" (MSH) Price Guide has published buyer prices for the following BDZs, up to 2015: diazepam, lorazepam, alprazolam. We have compiled supplier and buyer prices for each BDZ for the latest year available (2015). The MSH Pricing Guide did not contain data for all the other BDZs (except for midazolam which was not included as it is a BDZ used for preoperative medication and sedation for short-term procedures only). See below table 7 for most recently available lowest, median, and highest supplier and buyer prices in United States Dollars (USD). In table 8 we report costs for a wider selection of BDZs.

Table 7. Supplier and buyer prices for BDZs

Medication	**Year**	**Lowest Price (USD)**	**Highest Price (USD)**	**Median Price (USD)**
Diazepam 5 mg tab/cap (supplier)	2015	0.0027	0.0285	0.0096
Diazepam 5 mg tab/cap (buyer)	2015	0.0074	0.0152	0.0113
Lorazepam 1 mg tab/cap (supplier)	2015	N/A	N/A	N/A
Lorazepam 1 mg tab/cap (buyer)	2015	0.0211	0.2340	0.1412
Alprazolam 0.25 mg tab/cap (supplier)	2015	N/A	N/A	N/A
Alprazolam 0.25 mg tab/cap (buyer)	2015	1 supplier only (OECS/PPS) selling at 0.004		

Source: MSH International Medical Products Price Guide - https://msh.org/resources/international-medical-products-price-guide/

Table 8. Costs for selected BDZs

preparation	brand name	Cost (USD)
Diazepam	Valium	Tablet: Brand: 2 mg (100): $327.06 5 mg (100): $508.68 10 mg (100): $856.28 Generic: 2 mg (100): $10.45 5 mg (100): $16.35 10 mg (100): $31.25 Liquid (5 mg/5 mL, 500-mL bottle): Generic only: $67.83
Lorazepam	Ativan	Tablet: Brand: 0.5 mg (100): $898.14 1 mg (100): $1199.78 2 mg (100): $1912.10 Generic: 0.5 mg (100): $67.75

		1 mg (100): $88.25 2 mg (100): $128.45 Liquid (2 mg/1 mL, 30-mL bottle): Generic only: $39.60
Alprazolam	Xanax	Tablets: Brand: 0.25 mg (100): $241.39 0.5 mg (100): $300.72 1 mg (100): $410.72 2 mg (100): $682.27 Generic: 0.25 mg (100): $69.50 0.5 mg (60): $128.95 1 mg (60): $160.40 2 mg (60): $212.90 3 mg (60): $319.35 ER Tablets: Brand: 0.5 mg (60): $299.93 1 mg (60): $373.20 2 mg (60): $495.34 3 mg (60): $742.93 Generic: 0.5 mg (60): $135.40 1 mg (60): $168.46 2 mg (60): $223.58 3 mg (60): $335.36 ODT (generic only): 0.25 mg (100): $218.26 0.5 mg (100): $271.93 1 mg (100): $362.81 2 mg (100): $616.91 Liquid (1 mg/mL, 30-mL bottle): Generic only: $81.05
Chlordiazepoxide	Librium	5 mg (100): $35.25 10 mg (100): $39.78 25 mg (100): $42.84
Clonazepam	Klonopin	Tablets: Brand: 0.5 mg (100): $245.48 1 mg (100): $280.03 2 mg (100): $388.01 Generic: 0.5 mg (100): $74.95 1 mg (100): $85.55 2 mg (100): $118.45 ODT: Generic: 0.125 mg (60): $77.93 0.25 mg (60): $77.93 0.5 mg (60): $77.80 1 mg (60): $88.91 2 mg (60): $123.19

Oxazepam	Serax	10 mg (100): $115.19 15 mg (100): $145.45 30 mg (100): $210.39

Source: "The Johns Hopkins Psychiatry Guide"[46]

10.2 Comparative cost-effectiveness data

There are no comparative cost-effectiveness studies among single BDZ compounds.

Most studies in the anxiety disorder research area comprehensibly focus on the comparative cost-effectiveness of different class of medicines for the long-term treatment of anxiety disorders. There is evidence indicating CBT or the combination of CBT and SSRIs as the most cost-effective interventions.[81]

Evidence suggests benzodiazepines may be associated with unnecessary costs from medicine ingredient costs, dispensing costs and consultation costs due to misuse and unnecessary prescribing. In a study of the United Kingdom National Health System, 67–72% of total costs related to BZDs were estimated to be unnecessary with a total unnecessary cost over three years (April 2015-March 2018) of £115,588,439 to £129,870,520 and a mean yearly unnecessary cost of £38,529,480 to £43,290,173.[82] In adults with generalized anxiety disorder, evidence also suggests long-term BZD use increases health care costs significantly. In a retrospective cohort study of 866 adults in the United States also indicated that mean total healthcare costs increased by $2334 following the initiation of a long-term (>90 days) course of treatment with a BZD treatment (from $4637 [SD=$9840] pre-treatment to $6971 [$17,002] posttreatment; $p<0.01$). Costs related to use of BDZs increased by an average of $1099, due to accident-related encounters (e.g., for treatment of fractures) and care received for other reasons possibly related to BDZ use (e.g., sedation, dizziness).[83] Another study employed a cost-utility analysis methodology to determine the economic impact of drugs commonly involved in potentially inappropriate prescribing in adults aged ≥65 years.[84] The study found that inappropriate prescribing of BDZs led to the largest reduction in QALYs (−0.07 QALYs) and incremental cost (€3470) in comparison with other medications subject to potentially inappropriate prescribing (non-steroidal anti-inflammatory drugs, and proton pump inhibitors).

It is generally considered that BDZs are not cost-effective in the long-term, and this fact seems to strengthen the rationale to limit the indication for diazepam and lorazepam to short-term periods only.

11. Regulatory status, market availability and pharmacopoieal standards

As described in section 7, diazepam was the second BDZ (Diazepam) ever to be released in 1963 by Hoffman la Roche Lorazepam (Ativan, Tavor) was approved by FDA on September 30, 1977 for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms. Diazepam and lorazepam are currently off-patent and generic formulations are available globally.

Pharmacopoeial standards: results for diazepam and lorazepam

(a) United States Pharmacopoeia: (Yes. Source: United States Pharmacopoeia)[1]

(b) British Pharmacopoeia: (Yes. Source: British Pharmacopeia)[2]

(c) European Pharmacopoeia: (Yes. Source: European Pharmacopeia Online 9.7)[3]

(d) Japanese Pharmacopoeia: (Unavailable. Source: Japanese Pharmacopeia 17th Edition)[4]

(e) International Pharmacopoeia: (Unavailable. Source: WHO Pharmacopeia Library)[5]

For reference, results for diazepam and lorazepam

Table 9. Availability of reference standards per commonly used pharmacopoeias

	Availability in commonly used pharmacopoeias				
Medication	United States	British	European	Japan	International
Diazepam	yes	yes	yes	yes	yes
Lorazepam	yes	yes	yes	yes	no

[1] United States Pharmacopoeia http://www.usp.org/
[2] British Pharmacopoeia https://www.pharmacopoeia.com/
[3] European Pharmacopoeia Online 9.7. http://online6.edqm.eu/ep907/
[4] Japanese Pharmacopoeia, 17th Edition https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0020.html
[5] WHO Pharmacopoeia Library http://apps.who.int/phint/en/p/docf/

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13. Appendices

APPENDIX 1: List of benzodiazepines under international control according to the European Monitoring Centre for Drugs and Drug Addiction

(https://www.emcdda.europa.eu/publications/drug-profiles/benzodiazepines_en)

Name	Duration of action	Major trade name
Sedative/hypnotics		
Brotizolam	Short	Lendormin
Estazolam	Intermediate	Pro-Som
Flunitrazepam	Short/Intermediate	Rohypnol
Flurazepam	Long	Dalmane
Haloxazolam	Long	Somelin
Loprazolam	Intermediate	Dormonoct
Lormetazepam	Short	Noctamid
Midazolam	Short	Versed
Nimetazepam	Long	Erinin
Nitrazepam	Intermediate	Mogadon
Temazepam	Short	Normison
Triazolam	Short	Halcion
Anxiolytics		
Alprazolam	Short	Xanax
Bromazepam	Long	Lexotan
Camazepam		Albego
Chlordiazepoxide	Long	Librium
Clobazam	Long	Frisium
Clonazepam	Intermediate	Rivotril
Clorazepate	Long	Tranxene
Clotiazepam	Short	Trecalmo
Cloxazolam	Long	Sepazon
Delorazepam	Long	En
Diazepam	Long	Valium
Ethyl hoflazepate	Long	Meilax
Fludiazepam	Short	Erispan
Halazepam	Long	Pacinone
Ketazolam	Long	Anseren
Lorazepam	Short/Intermediate	Ativan
Medazepam	Long	Nobrium
Nordazepam	Long	Stilny
Oxazepam	Short	Serax
Oxazolam	Long	Tranquit
Pinazepam	Long	Domar
Prazepam	Long	Centrax
Tetrazepam	Short	Clinoxan

APPENDIX 2. List compounds classified as benzodiazepines in the WHO ATC list (https://www.whocc.no/atc_ddd_index/)

N NERVOUS SYSTEM **N05** PSYCHOLEPTICS **N05C** HYPNOTICS AND SEDATIVES **N05CD** Benzodiazepine derivatives		**N** NERVOUS SYSTEM **N05** PSYCHOLEPTICS **N05B** ANXIOLYTICS **N05BA** Benzodiazepine derivatives	
N05CD01	flurazepam	N05BA01	diazepam
N05CD02	nitrazepam	N05BA02	chlordiazepoxide
N05CD03	flunitrazepam	N05BA03	medazepam
N05CD04	estazolam	N05BA04	oxazepam
N05CD05	triazolam	N05BA05	potassium clorazepate
N05CD06	lormetazepam	N05BA06	lorazepam
N05CD07	temazepam	N05BA07	adinazolam
N05CD08	midazolam	N05BA08	bromazepam
N05CD09	brotizolam	N05BA09	clobazam
N05CD10	quazepam	N05BA10	ketazolam
N05CD11	loprazolam	N05BA11	prazepam
N05CD12	doxefazepam	N05BA12	alprazolam
N05CD13	cinolazepam	N05BA13	halazepam
N05CD14	remimazolam	N05BA14	pinazepam
N05CD15	nimetazepam	N05BA15	camazepam
		N05BA16	nordazepam
		N05BA17	fludiazepam
		N05BA18	ethyl loflazepate
		N05BA19	etizolam
		N05BA21	clotiazepam
		N05BA22	cloxazolam
		N05BA23	tofisopam
		N05BA24	bentazepam
		N05BA25	mexazolam
		N05BA56	lorazepam, combinations