



Topic Brief: Safe Use of Prescription Benzodiazepines

Date: 2/10/2023

Nomination Number: 1007

Purpose: This document summarizes the information addressing a nomination submitted on June 3, 2022, through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue: Benzodiazepine receptor agonists (BZRAs) are associated with misuse-related morbidity and mortality. The nominators for this topic request an AHRQ-generated systematic review for the development of evidence-based guidelines on appropriate prescribing of these medications.

Findings: The EPC Program will not develop a new systematic review because we found systematic reviews addressing most of the concerns of this nomination and no evidence for the remainder of the scope.

Background

Benzodiazepines (BZDs) are sedative-hypnotic medications that are FDA-approved to treat generalized anxiety disorder, insomnia, seizures, social phobia, and panic disorder.¹ Data from the 2014-2016 indicated that BZDs were most commonly prescribed for mental disorders, and BZDs plus opioids were most commonly prescribed for musculoskeletal system and connective tissue diseases.² BZDs belong to a larger class of drugs called BZRAs, which also includes Z-drugs. Z-drugs were introduced to the market in the 1990s and have only been approved for insomnia.³ The estimated annual costs of insomnia in the United States range between \$30 and \$107 billion.⁴ Expenditures for benzodiazepines in Medicaid beneficiaries were \$171.1 million in 2009.⁵

In the United States between 2015 and 2016, 12.6 percent of Americans reported past year BZD use annually, and 17.7 percent of BZD use was misuse without a prescription and obtained from a friend or relative. Among those ≥ 50 years old, BZDs were more likely to be used more often than prescribed to facilitate sleep.⁶ In 2020, 16 percent of overdose deaths involving opioids also involved benzodiazepines.⁷ Factors associated with misuse include other substance use, receipt of benzodiazepine prescription, and psychiatric symptoms and disorders. Misuse is associated with mortality, poor self-reported quality of life, criminality, and continued substance use during treatment.⁸ The nominators are requesting an AHRQ-generated systematic review to be used to develop an evidence-based guideline. They state that there are many guidelines, but they vary and do not address problems associated with long-term use.

Scope

1. What is the effectiveness and harms of benzodiazepine receptor agonists (BZRAs)?
2. How does comprehensive informed consent to BZRA treatment affect outcomes?

Table 1. Questions and PICOs (population, intervention, comparator, and outcome).

Questions	Effectiveness and harms of BZRAs	Informed consent to BZRA treatment
Population	Adults with 1) insomnia; 2) anxiety Subgroups: <ul style="list-style-type: none"> • Age • Indication and/or associated diagnosis • Previous use of BZRAs • History of substance misuse and/or use disorder • Concurrent prescription opioid use • History of PTSD or TBI • Pregnancy/neonatal abstinence syndrome 	BZRA-naïve adult patients being prescribed BZRA; current BZRA adult patients being prescribed BZRA
Interventions	Benzodiazepines for 1) insomnia, 2) anxiety; Z-drugs for insomnia Subgroups: <ul style="list-style-type: none"> • duration of use • peak dose • Type of BZRA • Follow-up post-discontinuation of BZRA <ul style="list-style-type: none"> ○ < 1 month ○ 1 month – 12 months ○ > 12 months 	Any intervention to facilitate the delivery of comprehensive informed consent (e.g., metrics to determine patient comprehension)
Comparators	Other pharmacological intervention, non-pharmacological intervention (e.g., CBT-insomnia, CBT for anxiety), placebo/no treatment Separate comparisons by time: <ul style="list-style-type: none"> • Prior to use • During active use • While discontinuing Post-discontinuation	Treatment as usual
Outcomes	Psychological/sleep assessment scores (e.g., GAD-7, HAM-A); quality of life scale Harms- physical dependence (tolerance, withdrawal during de-prescription, long-duration tapering (>= 2 months) required to manage withdrawal symptoms, continuing post-deprescription withdrawal-like	<ul style="list-style-type: none"> • BZRA-naïve patients - rejection of BZRA therapy • current BZRA patients – attempts to discontinue BZRA • All BZRA addiction/dependence/misuse

	symptoms), misuse, addiction, overdose, falls, MVAs, cognitive impairment	
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Abbreviations: CBT=cognitive behavioral therapy; BZRA=benzodiazepine receptor agonist; GAD-7=generalized anxiety disorder-7 questionnaire; HAM-A=Hamilton anxiety rating scale; MVA=motor vehicle accidents; PTSD=post-traumatic stress disorder; TBI=traumatic brain injury.

Assessment Methods

See Appendix A.

Summary of Literature Findings

We found two systematic reviews addressing Key Question 1 and very little evidence addressing Key Question 2.

For Key Question 1, we found a 2022 systematic review and meta-analysis addressing the insomnia disorder population for Key Question 1 titled “Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis”⁹. This review compared the effectiveness of different pharmacological treatments, including benzodiazepines and Z-drugs, for the treatment of acute and long-term treatment of adults with insomnia disorder. For the anxiety disorder population, we found a 2022 systematic review and meta-analysis titled “Drug treatment for panic disorder with or without agoraphobia: systematic review and network meta-analysis of randomized controlled trials.”¹⁰ This review compared a range of drug classes, including benzodiazepines, used to treat panic disorder with or without agoraphobia to determine those with the highest rates of remission and lowest risk of adverse events.

For Key Question 2, we found a 2021 systematic review titled “Benzodiazepine deprescription strategies in chronic users: a systematic review.”¹¹ This review evaluated strategies to facilitate deprescription of benzodiazepines, such as patient-education focused interventions, but does not include studies of benzodiazepine-naïve patients being consented for benzodiazepine use. We did not find any primary studies addressing consent to BZRAs in BZRA-naïve patients.

Table 2. Literature identified for each Key Question

Question	Systematic reviews (10/2019-10/2022)	Primary studies (10/2017-10/2022)
Effectiveness and harms of BZRAs	Total: 2 ^{9, 10}	NA
Informed consent to BZRA treatment	Total: 1 ¹¹	Total: 0

Abbreviations: BZRA=benzodiazepine receptor agonist; NA=not applicable.

See Appendix B for detailed assessments of all EPC selection criteria.

Summary of Selection Criteria Assessment

BZRAs are commonly misused, so guidance on safe and effective prescribing is important. Recent systematic reviews addressing the comparative effectiveness of pharmacological interventions for insomnia and panic disorder have been conducted. A new systematic review overlapping these areas would likely be of limited impact.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

References

1. Benzodiazepine Drug Information. US Food and Drug Administration. doi: <https://www.fda.gov/drugs/information-drug-class/benzodiazepine-drug-information>.
2. Santo L, Rui P, Ashman JJ. Physician Office Visits at Which Benzodiazepines Were Prescribed: Findings From 2014-2016 National Ambulatory Medical Care Survey. *Natl Health Stat Report*. 2020 Jan(137):1-16. doi: <https://www.cdc.gov/nchs/data/nhsr/nhsr137-508.pdf>. PMID: 32510318.
3. Brandt J, Leong C. Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. *Drugs R D*. 2017 Dec;17(4):493-507. doi: <https://doi.org/10.1007/s40268-017-0207-7>. PMID: 28865038.
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5. Gorevski E, Bian B, Kelton CM, et al. Utilization, spending, and price trends for benzodiazepines in the US Medicaid program: 1991-2009. *Ann Pharmacother*. 2012 Apr;46(4):503-12. doi: <https://doi.org/10.1345/aph.1Q618>. PMID: 22454448.
6. Maust DT, Lin LA, Blow FC. Benzodiazepine Use and Misuse Among Adults in the United States. *Psychiatr Serv*. 2019 Feb 1;70(2):97-106. doi: <https://doi.org/10.1176/appi.ps.201800321>. PMID: 30554562.
7. Benzodiazepines and Opioids. National Institutes of Health. doi: <https://nida.nih.gov/research-topics/opioids/benzodiazepines-opioids>.
8. Votaw VR, Geyer R, Rieselbach MM, et al. The epidemiology of benzodiazepine misuse: A systematic review. *Drug Alcohol Depend*. 2019 Jul 1;200:95-114. doi: <https://doi.org/10.1016/j.drugalcdep.2019.02.033>. PMID: 31121495.
9. De Crescenzo F, D'Alo GL, Ostinelli EG, et al. Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis. *Lancet*. 2022 07 16;400(10347):170-84. doi: [https://dx.doi.org/10.1016/S0140-6736\(22\)00878-9](https://dx.doi.org/10.1016/S0140-6736(22)00878-9). PMID: 35843245.
10. Chawla N, Anothaisintawee T, Charoenrungrueangchai K, et al. Drug treatment for panic disorder with or without agoraphobia: systematic review and network meta-analysis of randomised controlled trials. *BMJ*. 2022 01 19;376:e066084. doi: <https://dx.doi.org/10.1136/bmj-2021-066084>. PMID: 35045991.
11. Ribeiro PRS, Schindwein AD. Benzodiazepine deprescription strategies in chronic users: a systematic review. *Family Practice*. 2021 09 25;38(5):684-93. doi: <https://dx.doi.org/10.1093/fampra/cmab017>. PMID: 33907803.
12. Kurko TA, Saastamoinen LK, Tähkää S, et al. Long-term use of benzodiazepines: Definitions, prevalence and usage patterns - a systematic review of register-based studies. *Eur Psychiatry*. 2015 Nov;30(8):1037-47. doi: <https://doi.org/10.1016/j.eurpsy.2015.09.003>. PMID: 26545257.

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years October 24, 2022 the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
 - AHRQ Evidence Reports <https://www.ahrq.gov/research/findings/evidence-based-reports/index.html>
 - EHC Program <https://effectivehealthcare.ahrq.gov/>
 - US Preventive Services Task Force <https://www.uspreventiveservicestaskforce.org/>
 - AHRQ Technology Assessment Program <https://www.ahrq.gov/research/findings/ta/index.html>
- US Department of Veterans Affairs Products publications
 - Evidence Synthesis Program <https://www.hsrd.research.va.gov/publications/esp/>
 - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program <https://www.healthquality.va.gov/>
- Cochrane Systematic Reviews <https://www.cochranelibrary.com/>
- PROSPERO Database (international prospective register of systematic reviews and protocols) <http://www.crd.york.ac.uk/prospero/>
- PubMed <https://www.ncbi.nlm.nih.gov/pubmed/>
- Joanna Briggs Institute <http://joannabriggs.org/>
- Epistemonikos <https://www.epistemonikos.org>

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a limited literature search in PubMed from the last five years October 24, 2017-October 24, 2022 on parts of the nomination scope not addressed by earlier identified systematic reviews. Because a large number of articles were identified, we reviewed a random sample of 200 titles and abstracts for each question for inclusion. We classified identified studies by question and study design, to assess the size and scope of a potential evidence review. We then calculated the projected total number of included studies based on the proportion of studies included from the random sample.

Search strategy

Ovid MEDLINE(R) ALL <1946 to October 21, 2022>

Date searched: October 24, 2022

- 1 exp benzodiazepine/ or exp benzodiazepine derivative/ or exp benzodiazepine receptor stimulating agent/ (68782)
- 2 (z-drug* or z drug*).ti,ab,kf. (454)
- 3 Eszopiclone/ or (eszopiclone or estorra or lunesta).ti,ab,kf. (317)
- 4 (Zopiclone or zopiclon* or imovane or limovan or nu-zopiclone or optidorm or rp 27 267 or rhovane or siaten or somnosan or ximovan or zileze or zimoclone or zop or zopi-puren or zopicalm* or zopitan or zoreclone or zopiclodura).ti,ab,kf. (1059)
- 5 Zolpidem/ or (Zolpidem* or ambien or amsic or bikalm or dalparan or "sl 80 0750" or sl 800750 23 n or sl-800750-23-n or stilnoct or stilnox or zodormdura or zoldem or zolirin or zolpi lich or zolpi-lich or zolpimist or zolpinox).ti,ab,kf. (2759)
- 6 (Zaleplon or zaleplon or sonata or cl 284,846 or cl 284846 or cl-284846 or cl284,846 or l 846 or l-846 or skp-1041 or starnoc or zelepion).ti,ab,kf. (691)
- 7 (Benzodiazepine* or BZD\$1 or BZRA\$1).ti,ab,kf. (37813)
- 8 (Alprazolam or alprazolam or xanor or alprox or apo alpraz or apo-alpraz or cassadan or d-65mt or d65mt or esparon or kalma or novo alprazol or novo-alprazol or nu alpraz or nu-alpraz or ralozam or tafil or trunkimazin or u-31,889 or u31,889 or xanax).ti,ab,kf. (2588)
- 9 (Bromazepam or anxyrex or apo bromazepam or apo-bromazepam or beta, bromazepam or bromalich or bromaz 1a 3667 12 pharma or bromazanyl or bromazep von ct or bromazepam al or bromazepam beta or bromazepam heumann or bromazepam neuraxpharm or bromazepam ratiopharm or bromazepam-neuraxpharm or bromazepam-ratiopharm or durazanyl or gen bromazepam or gen-bromazepam or lexatin or lexiomil or lexotan or lexotanil or ro 5-3350 or ro 53350 or von ct, bromazep).ti,ab,kf. (553)
- 10 (Chlordiazepoxide or chlordiaepoxide or chlordiaepoxide hydrobromide or chlordiaepoxide hydrochloride or chlordiaepoxide monohydrochloride or chlordiaepoxide perchlorate or chlozepid or elenium or hydrobromide, chlordiaepoxide or hydrochloride, chlordiaepoxide or librium or methaminodiazepoxide or monohydrochloride, chlordiaepoxide or perchlorate, chlordiaepoxide).ti,ab,kf. (3463)
- 11 (Clobazam or perizam or tapclob or zacco or frisium or hr 376 or lm 2717 or lm-2717 or lm2717 or onfi or urbanyl).ti,ab,kf. (1289)
- 12 (Clonazepam or klonopin or antelepsin or rivotril or ro 5-4023 or ro 54023).ti,ab,kf. (4008)
- 13 (Clorazepate or tranxene or 4306-cb or chlorazepate or clorazepate dipotassium or clorazepate monopotassium or clorazepic acid or dipotassium chlorazepate or tranxilium).ti,ab,kf. (461)
- 14 (Diazepam or valium or apaurin or diazemuls or faustan or relanium or seduxen or sibazon or stesolid).ti,ab,kf. (21124)
- 15 (Estazolam or d-40ta or d40ta or nuctalon or prosom or tasedan).ti,ab,kf. (279)
- 16 (Flunitrazepam or fluni 1a pharma or flunibeta or flunimerck or fluninoc or flunitrazepam neuraxpharm or flunitrazepam ratiopharm or flunitrazepam teva or flunitrazepam-neuraxpharm or flunitrazepam-ratiopharm or flunitrazepam-teva or flunizep von ct or fluridrazepam or narcozep or ro-5-4200 or ro54200 or rohipnol or rohypnol or von ct, flunizep).ti,ab,kf. (3238)
- 17 (Flurazepam or apo flurazepam or apo-flurazepam or dalmadorm or dalmane or dihydrochloride, flurazepam or dormodor or flurazepam dihydrochloride or flurazepam hydrochloride or flurazepam mono perchlorate or flurazepam mono-perchlorate or flurazepam monohydrochloride or hydrochloride, flurazepam or mono-perchlorate, flurazepam or monohydrochloride, 5087 flurazepam or staurodorm).ti,ab,kf. (962)
- 18 (Halazepam or paxipam or alapryl or pacinone).ti,ab,kf. (56)
- 19 (Ketazolam or anxon or anseren or ansieten or ansietil or atenuel or lofran or marcen or sedatival fp or sedavital or sedotime or solatran or unakalm or mi 49001 or marcen or u 28774).ti,ab,kf. (39)
- 20 (Loprazolam or dormonoc).ti,ab,kf. (77)
- 21 (Lorazepam or apo lorazepam or apo-lorazepam or Ativan or donix or duralozam or durazolam or idalprem or laubeel or lorazep von ct or lorazepam medical or lorazepam neuraxpharm or lorazepam ratiopharm or lorazepam-neuraxpharm or lorazepam-ratiopharm or medical, lorazepam or novo lorazem or novo-lorazem or nu loraz or nu-loraz or orfidal wyeth or sedicepan or sinestron or somagerol or temesta or tavor or tolid or von ct, lorazep or wy 4036 ot wy-4036 or wy4036 or wyeth, orfidal).ti,ab,kf. (4095)

22 (Lormetazepam or noctamid or methylorazepam or n-methylorazepam or noctamid or loramet).ti,ab,kf. (264)

23 (Medazepam or hydrochloride, medazepam or medazepam awd or medazepam hydrochloride or medazepam monohydrochloride or monohydrochloride, medazepam or nobrium or ro 5 4556 or ro 5-4556 or ro 54556 or rudotel or rusedal).ti,ab,kf. (242)

24 (Nitrazepam or alodorm or dormalon or dormo-puren or eatan or imadorm or imeson or mogadon or nitrazadon or nitrazep or nitrazepam al or nitrazepam neuraxpharm or nitrazepam-neuraxpharm or nitrodiazepam or novanox or radedorm or remnos or rhoxal nitrazepam or rhoxal-nitrazepam or serenade or somnite).ti,ab,kf. (1110)

25 (Nordazepam or calmday or dealkylprazepam or demethyldiazepam or deoxydemoxepam or desmethylidiazepam or n desalkylhalazepam or n descyclopropylmethyl prazepam or n descyclopropylmethylprazepam or n destrifluoroethylhalazepam or n-desalkylhalazepam or n-descyclopropylmethyl-prazepam or n-descyclopropylmethylprazepam or n-destrifluoroethylhalazepam or nordaz or nordiazepam or norprazepam or ro 5 2180 or ro 5-2180 or ro 52180 or tranxilium n or vegesan).ti,ab,kf. (798)

26 (Oxazepam or serenid or serepax or seresta or adumbran or serax or tazepam).ti,ab,kf. (1587)

27 (Prazepam or centrax or demetrin or lysanxia or mono demetrin or prazepam or reepam).ti,ab,kf. (206)

28 (Quazepam or doral or prosedar or quazium or dormalin or oniria or quazepam or cetrane or quiedorm or sch 16134 or sch-16134).ti,ab,kf. (170)

29 (Temazepam or 3 hydroxydiazepam or 3-hydroxydiazepam or apo temazepam or apo-temazepam or dasuen or euhypnos or gen temazepam or gen-temazepam or hydroxydiazepam or levaxol or methyloxazepam or nocturne or norkotral tema or normison or normitab or nortem or novo temazepam or novo-temazepam or nu temazepam or nu-temazepam or oxydiazepam or pms temazepam or pms-temazepam or planum or pronervon t or remestan or restoril or ro 5 5345 or ro-5-5345 or ro55345 or sah 47 603 or sah 47-603 or sah 47603 or signopam or tema, norkotral or temaze or temazep von ct or temtabs or tenox or von ct, temazep or wy 3917 or wy-3917 or wy3917).ti,ab,kf. (2512)

30 (Triazolam or apo triazo or apo-triazo or gen triazolam or gen-triazolam or halcion or trilam or u 33,030 or u-33,030 or u33,030).ti,ab,kf. (1616)

31 or/1-30 (99181)

32 *Anxiety/ or exp *Anxiety Disorders/ or *"Sleep Initiation and Maintenance Disorders"/ (117478)

33 (anxiety or anxiolytic\$1 or insomnia\$2).ti,kf. (99453)

34 or/32-33 (158279)

35 and/31,34 (9174)

36 35 not ((Animals/ not Humans/) or (animal\$1 or canine or cat\$1 or dog\$ or feline or hamster\$1 or mice or mouse or rat\$1 or rattus or rodent\$4).ti. or ("case reports" or editorial or letter or news).pt.) (6022)

37 limit 36 to english language 5052)

38 limit 37 to yr="2019 -Current" (543)

39 (meta-analysis or "systematic review").pt. or (meta-anal* or metaanal* or ((evidence or scoping or systematic or umbrella) adj4 (review or synthesis))).ti. (375337)

40 and/38-39 (64)

41 limit 37 to yr="2017 -Current" (815)

42 ("controlled clinical trial" or "randomized controlled trial").pt. or (control\$3 or placebo\$1 or random* or trial).ti,ab. (5306785)

43 and/41-42 (351)

44 43 not 40 (296)

45 exp cohort studies/ or exp epidemiologic studies/ or (cohort or "controlled before-after" or cross-sectional or follow-up* or "interrupted time series" or longitudinal\$3 or prospective\$2 or retrospective\$2).ti,ab,kf. (4442212)

46 and/41,45 (275)

47 46 not (40 or 44) (151)

EBM Reviews - Cochrane Central Register of Controlled Trials September 2022

Date searched: October 24, 2022

- 1 exp benzodiazepine/ or exp benzodiazepine derivative/ or exp benzodiazepine receptor stimulating agent/ (9909)
- 2 (z-drug* or z drug*).ti,ab. (31)
- 3 Eszopiclone/ or (eszopiclone or estorra or lunesta).ti,ab. (210)
- 4 (Zopiclone or zopiclon* or imovane or limovan or nu-zopiclone or optidorm or rp 27 267 or rhovane or siaten or somnosan or ximovan or zileze or zimoclone or zop or zopi-puren or zopicalm* or zopitan or zorclone or zopiclodura).ti,ab. (377)
- 5 Zolpidem/ or (Zolpidem* or ambien or amsic or bikalm or dalparan or "sl 80 0750" or sl 800750 23 n or sl-800750-23-n or stilnoct or stilnox or zodormdura or zoldem or zolirin or zolpi lich or zolpi-lich or zolpimist or zolpinox).ti,ab. (905)
- 6 (Zaleplon or zaleplon or sonata or cl 284,846 or cl 284846 or cl-284846 or cl284,846 or l 846 or l-846 or skp-1041 or starnoc or zelepion).ti,ab. (193)
- 7 (Benzodiazepine* or BZD\$1 or BZRA\$1).ti,ab. (4722)
- 8 (Alprazolam or alprazolam or xanor or alprox or apo alpraz or apo-alpraz or cassadan or d-65mt or d65mt or esparon or kalma or novo alprazol or novo-alprazol or nu alpraz or nu-alpraz or ralozam or tafil or frankimazin or u-31,889 or u31,889 or xanax).ti,ab. (1024)
- 9 (Bromazepam or anxyrex or apo bromazepam or apo-bromazepam or beta, bromazepam or bromalich or bromaz 1a 3667 12 pharma or bromazanil or bromazepam von ct or bromazepam al or bromazepam beta or bromazepam heumann or bromazepam neuraxpharm or bromazepam ratiopharm or bromazepam-neuraxpharm or bromazepam-ratiopharm or durazanil or gen bromazepam or gen-bromazepam or lexatin or lexiomil or lexotan or lexotanil or ro 5-3350 or ro 53350 or von ct, bromazepam).ti,ab. (234)
- 10 (Chlordiazepoxide or chlordiazepoxide or chlordiazepoxide hydrobromide or chlordiazepoxide hydrochloride or chlordiazepoxide monohydrochloride or chlordiazepoxide perchlorate or chlozepid or elenium or hydrobromide, chlordiazepoxide or hydrochloride, chlordiazepoxide or librium or methaminodiazepoxide or monohydrochloride, chlordiazepoxide or perchlorate, chlordiazepoxide).ti,ab. (337)
- 11 (Clobazam or perizam or tapclob or zacco or frisium or hr 376 or lm 2717 or lm-2717 or lm2717 or onfi or urbanyl).ti,ab. (323)
- 12 (Clonazepam or klonopin or antelepsin or rivotril or ro 5-4023 or ro 54023).ti,ab. (432)
- 13 (Clorazepate or tranxene or 4306-cb or chlorazepate or clorazepate dipotassium or clorazepate monopotassium or clorazepic acid or dipotassium chlorazepate or tranxilium).ti,ab. (162)
- 14 (Diazepam or valium or apaurin or diazemuls or faustan or relanium or seduxen or sibazon or stesolid).ti,ab. (3600)
- 15 (Estazolam or d-40ta or d40ta or nuctalon or prosom or tasedan).ti,ab. (140)
- 16 (Flunitrazepam or fluni 1a pharma or flunibeta or flunimerck or fluninoc or flunitrazepam neuraxpharm or flunitrazepam ratiopharm or flunitrazepam teva or flunitrazepam-neuraxpharm or flunitrazepam-ratiopharm or flunitrazepam-teva or flunizep von ct or fluridrazepam or narcozep or ro-5-4200 or ro54200 or rohipnol or rohypnol or von ct, flunizep).ti,ab. (503)
- 17 (Flurazepam or apo flurazepam or apo-flurazepam or dalmadorm or dalmene or dihydrochloride, flurazepam or dormodor or flurazepam dihydrochloride or flurazepam hydrochloride or flurazepam mono perchlorate or flurazepam mono-perchlorate or flurazepam monohydrochloride or hydrochloride, flurazepam or mono-perchlorate, flurazepam or monohydrochloride, 5087 flurazepam or staurodorm).ti,ab. (244)
- 18 (Halazepam or paxipam or alapryl or pacinone).ti,ab. (20)
- 19 (Ketazolam or anxon or anseren or ansieten or ansietil or atenual or lofran or marcen or sedatival fp or sedavital or sedotime or solatran or unakalm or mi 49001 or marcen or u 28774).ti,ab. (37)
- 20 (Loprazolam or dormonoct).ti,ab. (41)

21 (Lorazepam or apo lorazepam or apo-lorazepam or Ativan or donix or duralozam or durazolam or idalprem or laubeel or lorazep von ct or lorazepam medical or lorazepam neuraxpharm or lorazepam ratiopharm or lorazepam-neuraxpharm or lorazepam-ratiopharm or medical, lorazepam or novo lorazem or novo-lorazem or nu loraz or nu-loraz or orfidal wyeth or sedicepan or sinestron or somagerol or temesta or tavor or tolid or von ct, lorazep or wy 4036 or wy-4036 or wy4036 or wyeth, orfidal).ti,ab. (1662)

22 (Lormetazepam or noctamid or methyllozepam or n-methyllozepam or noctamid or loramet).ti,ab. (169)

23 (Medazepam or hydrochloride, medazepam or medazepam awd or medazepam hydrochloride or medazepam monohydrochloride or monohydrochloride, medazepam or nobrium or ro 5 4556 or ro 5-4556 or ro 54556 or rudotel or rusedal).ti,ab. (67)

24 (Nitrazepam or alodorm or dormalon or dormo-puren or eatan or imadorm or imeson or mogadon or nitrazadon or nitrazep or nitrazepam al or nitrazepam neuraxpharm or nitrazepam-neuraxpharm or nitrodiazepam or novanox or radedorm or remnos or rhoxal nitrazepam or rhoxal-nitrazepam or serenade or somnite).ti,ab. (294)

25 (Nordazepam or calmday or dealkylprazepam or demethyldiazepam or deoxydemoxepam or desmethyldiazepam or n desalkylhalazepam or n descyclopropylmethyl prazepam or n descyclopropylmethylprazepam or n destrifluoroethylhalazepam or n-desalkylhalazepam or n-descyclopropylmethyl-prazepam or n-descyclopropylmethylprazepam or n-destrifluoroethylhalazepam or nordaz or nordiazepam or norprazepam or ro 5 2180 or ro 5-2180 or ro 52180 or tranxilium n or vegesan).ti,ab. (87)

26 (Oxazepam or serenid or serepax or seresta or adumbran or serax or tazepam).ti,ab. (305)

27 (Prazepam or centrax or demetrin or lysanxia or mono demetrin or prazepam or reepam).ti,ab. (68)

28 (Quazepam or doral or prosedar or quazium or dormalin or oniria or quazepam or cetrane or quiedorm or sch 16134 or sch-16134).ti,ab. (69)

29 (Temazepam or 3 hydroxydiazepam or 3-hydroxydiazepam or apo temazepam or apo-temazepam or dasuen or euhypnos or gen temazepam or gen-temazepam or hydroxydiazepam or levaxol or methyloxazepam or nocturne or norkotral tema or normison or normitab or nortem or novo temazepam or novo-temazepam or nu temazepam or nu-temazepam or oxydiazepam or pms temazepam or pms-temazepam or planum or pronervon t or remestan or restoril or ro 5 5345 or ro-5-5345 or ro55345 or sah 47 603 or sah 47-603 or sah 47603 or signopam or tema, norkotral or temaze or temazep von ct or temtabs or tenox or von ct, temazep or wy 3917 or wy-3917 or wy3917).ti,ab. (398)

30 (Triazolam or apo triazo or apo-triazo or gen triazolam or gen-triazolam or halcion or trilam or u 33,030 or u-33,030 or u33,030).ti,ab. (619)

31 or/1-30 (17998)

32 *Anxiety/ or exp *Anxiety Disorders/ or *"Sleep Initiation and Maintenance Disorders"/ (4649)

33 (anxiety or anxiolytic\$1 or insomnia\$2).ti. (20591)

34 or/32-33 (23409)

35 and/31,34 (2520)

36 35 not ((Animals/ not Humans/) or (animal\$1 or canine or cat\$1 or dog\$ or feline or hamster\$1 or mice or mouse or rat\$1 or rattus or rodent\$4).ti. or ("case reports" or editorial or letter or news).pt.) (2501)

37 limit 36 to english language (2271)

38 limit 37 to yr="2017 -Current" (325)

39 38 not ("trial registry record".pt. or NCT*.tn.) (223)

Date searched: October 24, 2022

- 1 benzodiazepines/ or alprazolam/ or benzodiazepine agonists/ or chlordiazepoxide/ or clonazepam/ or diazepam/ or flunitrazepam/ or flurazepam/ or lorazepam/ or midazolam/ or nitrazepam/ or oxazepam/ (11027)
- 2 (z-drug* or z drug*).ti,ab. (130)
- 3 (eszopiclone or estorra or lunesta).ti,ab. (118)
- 4 (Zopiclone or zopiclon* or imovane or limovan or nu-zopiclone or optidorm or rp 27 267 or rhovane or siaten or somnosan or ximovan or zileze or zimoclone or zop or zopi-puren or zopicalm* or zopitan or zorclone or zopiclodura).ti,ab. (306)
- 5 (Zolpidem* or ambien or amsic or bikalm or dalparan or "sl 80 0750" or sl 800750 23 n or sl-800750-23-n or stilnoct or stilnox or zodormdura or zoldem or zolirin or zolpi lich or zolpi-lich or zolpimist or zolpinox).ti,ab. (968)
- 6 (Zaleplon or zaleplon or sonata or cl 284,846 or cl 284846 or cl-284846 or cl284,846 or l 846 or l-846 or skp-1041 or starnoc or zelepion).ti,ab. (284)
- 7 (Benzodiazepine* or BZD\$1 or BZRA\$1).ti,ab. (12500)
- 8 (Alprazolam or alprazolan or xanor or alprox or apo alpraz or apo-alpraz or cassadan or d-65mt or d65mt or esparon or kalma or novo alprazol or novo-alprazol or nu alpraz or nu-alpraz or ralozam or tafil or frankimazin or u-31,889 or u31,889 or xanax).ti,ab. (1368)
- 9 (Bromazepam or anxyrex or apo bromazepam or apo-bromazepam or beta, bromazepam or bromalich or bromaz 1a 3667 12 pharma or bromazanil or bromazep von ct or bromazepam al or bromazepam beta or bromazepam heumann or bromazepam neuraxpharm or bromazepam ratiopharm or bromazepam-neuraxpharm or bromazepam-ratiopharm or durazanil or gen bromazepam or gen-bromazepam or lexatin or lexomil or lexotan or lexotanil or ro 5-3350 or ro 53350 or von ct, bromazep).ti,ab. (149)
- 10 (Chlordiazepoxide or chlordiazepoxide or chlordiazepoxide hydrobromide or chlordiazepoxide hydrochloride or chlordiazepoxide monohydrochloride or chlordiazepoxide perchlorate or chlozepid or elenium or hydrobromide, chlordiazepoxide or hydrochloride, chlordiazepoxide or librium or methaminodiazepoxide or monohydrochloride, chlordiazepoxide or perchlorate, chlordiazepoxide).ti,ab. (1679)
- 11 (Clobazam or perizam or tapclob or zacco or frisium or hr 376 or lm 2717 or lm-2717 or lm2717 or onfi or urbanyl).ti,ab. (261)
- 12 (Clonazepam or klonopin or antelespin or rivotril or ro 5-4023 or ro 54023).ti,ab. (1312)
- 13 (Clorazepate or tranxene or 4306-cb or chlorazepate or clorazepate dipotassium or clorazepate monopotassium or clorazepic acid or dipotassium chlorazepate or tranxilium).ti,ab. (134)
- 14 (Diazepam or valium or apaurin or diazemuls or faustan or relanium or seduxen or sibazon or stesolid).ti,ab. (4938)
- 15 (Estazolam or d-40ta or d40ta or nuctalon or prosom or tasedan).ti,ab. (35)
- 16 (Flunitrazepam or fluni 1a pharma or flunibeta or flunimerck or fluninoc or flunitrazepam neuraxpharm or flunitrazepam ratiopharm or flunitrazepam teva or flunitrazepam-neuraxpharm or flunitrazepam-ratiopharm or flunitrazepam-teva or flunizep von ct or fluridrazepam or narcozep or ro-5-4200 or ro54200 or rohipnol or rohypnol or von ct, flunizep).ti,ab. (454)
- 17 (Flurazepam or apo flurazepam or apo-flurazepam or dalmadorm or dalmane or dihydrochloride, flurazepam or dormodor or flurazepam dihydrochloride or flurazepam hydrochloride or flurazepam mono perchlorate or flurazepam mono-perchlorate or flurazepam monohydrochloride or hydrochloride, flurazepam or mono-perchlorate, flurazepam or monohydrochloride, 5087 flurazepam or staurodorm).ti,ab. (275)
- 18 (Halazepam or paxipam or alapryl or pacinone).ti,ab. (20)
- 19 (Ketazolam or anxon or anseren or ansieten or ansietil or atenuat or lofran or marcen or sedatival fp or sedavital or sedotime or solatran or unakalm or mi 49001 or marcen or u 28774).ti,ab. (16)

20 (Loprazolam or dormonoct).ti,ab. (14)

21 (Lorazepam or apo lorazepam or apo-lorazepam or Ativan or donix or duralozam or durazolam or idalprem or laubeel or lorazep von ct or lorazepam medical or lorazepam neuraxpharm or lorazepam ratiopharm or lorazepam-neuraxpharm or lorazepam-ratiopharm or medical, lorazepam or novo lorazem or novo-lorazem or nu loraz or nu-loraz or orfidal wyeth or sedicepan or sinestron or somagerol or temesta or tavor or tolid or von ct, lorazep or wy 4036 ot wy-4036 or wy4036 or wyeth, orfidal).ti,ab. (1774)

22 (Lormetazepam or noctamid or methyllorazepam or n-methyllorazepam or noctamid or loramet).ti,ab. (62)

23 (Medazepam or hydrochloride, medazepam or medazepam awd or medazepam hydrochloride or medazepam monohydrochloride or monohydrochloride, medazepam or nobrium or ro 5 4556 or ro 5-4556 or ro 54556 or rudotel or rusedal).ti,ab. (57)

24 (Nitrazepam or alodorm or dormalon or dormo-puren or eatan or imadorm or imeson or mogadon or nitrazadon or nitrazep or nitrazepam al or nitrazepam neuraxpharm or nitrazepam-neuraxpharm or nitrodiazepam or novanox or radedorm or remnos or rhoxal nitrazepam or rhoxal-nitrazepam or serenade or somnite).ti,ab. (215)

25 (Nordazepam or calmday or dealkylprazepam or demethyldiazepam or deoxydemoxepam or desmethyldiazepam or n desalkylhalazepam or n descyclopropylmethyl prazepam or n descyclopropylmethylprazepam or n destrifluoroethylhalazepam or n-desalkylhalazepam or n-descyclopropylmethyl-prazepam or n-descyclopropylmethylprazepam or n-destrifluoroethylhalazepam or nordaz or nordiazepam or norprazepam or ro 5 2180 or ro 5-2180 or ro 52180 or tranxilium n or vegesan).ti,ab. (59)

26 (Oxazepam or serenid or serepax or seresta or adumbran or serax or tazepam).ti,ab. (348)

27 (Prazepam or centrax or demetrin or lysanxia or mono demetrin or prazepam or reepam).ti,ab. (36)

28 (Quazepam or doral or prosedar or quazium or dormalin or oniria or quazepam or cetrane or quiedorm or sch 16134 or sch-16134).ti,ab. (45)

29 (Temazepam or 3 hydroxydiazepam or 3-hydroxydiazepam or apo temazepam or apo-temazepam or dasuen or euhypnos or gen temazepam or gen-temazepam or hydroxydiazepam or levaxol or methyloxazepam or nocturne or norkotral tema or normison or normitab or nortem or novo temazepam or novo-temazepam or nu temazepam or nu-temazepam or oxydiazepam or pms temazepam or pms-temazepam or planum or pronervon t or remestan or restoril or ro 5 5345 or ro-5-5345 or ro55345 or sah 47 603 or sah 47-603 or sah 47603 or signopam or tema, norkotral or temaze or temazep von ct or temtabs or tenox or von ct, temazep or wy 3917 or wy-3917 or wy3917).ti,ab. (788)

30 (Triazolam or apo triazo or apo-triazo or gen triazolam or gen-triazolam or halcion or trilam or u 33,030 or u-33,030 or u33,030).ti,ab. (552)

31 or/1-30 (22320)

32 exp *Anxiety/ or *Anxiety Management/ or exp *Anxiety Disorders/ or *Insomnia/ (113287)

33 (anxiety or anxiolytic\$1 or insomnia\$2).ti. (67900)

34 or/32-33 (123403)

35 and/31,34 (4752)

36 35 not ((Animals/ not Humans/) or (animal\$1 or canine or cat\$1 or dog\$ or feline or hamster\$1 or mice or mouse or rat\$1 or rattus or rodent\$4).ti. or "case report*".ti. or ("column/opinion" or "comment/reply" or editorial or interview).dt.) (3793)

37 limit 36 to english language (3412)

38 limit 37 to yr="2019 -Current" (187)

39 38 and (("0830 systematic review" or 1200 meta analysis).md. or (meta-anal* or metaanal* or ((evidence or scoping or systematic or umbrella) adj4 (review or synthesis))).ti. (24)

40 limit 37 to yr="2017 -Current" (291)

41 40 and ("0300 clinical trial".md. or (control\$3 or placebo\$1 or random* or trial).ti,ab.) (120)
42 41 not 39 (98)
43 limit 40 to ("0400 empirical study" or "0430 followup study" or "0450 longitudinal study" or
"0451 prospective study" or "0453 retrospective study" or 1800
quantitative study or 2100 treatment outcome) (157)
44 40 and (cohort or "controlled before-after" or cross-sectional or follow-up* or "interrupted
time series" or longitudinal\$3 or prospective\$2 or retrospective\$2).ti,ab. (60)
45 or/43-44 (167)
46 45 not (39 or 42) (97)

EPISTEMONIKOS

Date searched: October 24, 2022

title:((benzodiazepine* OR z-drug* OR "z drug*" OR Eszopiclone OR Zopiclone OR Zolpidem*
OR Zaleplon OR Alprazolam OR Bromazepam OR Chlordiazepoxide OR Clobazam OR
Clonazepam OR Clorazepate OR Diazepam OR Estazolam OR Flunitrazepam OR Flurazepam
OR Halazepam OR Ketazolam OR Loprazolam OR Lorazepam OR Lormetazepam OR
Midazolam OR Nitrazepam OR Nordazepam OR Oxazepam OR Prazepam OR Quazepam OR
Temazepam OR Triazolam)) AND title:(anxiety OR insomn*) (37)

PROSPERO

Date searched: October 24, 2022

((((benzodiazepine* OR z-drug* OR "z drug*" OR Eszopiclone OR Zopiclone OR Zolpidem*
OR Zaleplon OR Alprazolam OR Bromazepam OR Chlordiazepoxide OR Clobazam OR
Clonazepam OR Clorazepate OR Diazepam OR Estazolam OR Flunitrazepam OR Flurazepam
OR Halazepam OR Ketazolam OR Loprazolam OR Lorazepam OR Lormetazepam OR
Midazolam OR Nitrazepam OR Nordazepam OR Oxazepam OR Prazepam OR Quazepam OR
Temazepam OR Triazolam) AND (anxiety OR insomn*))) :TI AND (Systematic Review OR
Meta-Analysis):RT WHERE CD FROM 24/10/2019 TO 24/10/2022 (14)

[ClinicalTrials](#)

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the United States?	Yes.
1b. Is the nomination a request for an evidence report?	Yes.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes. In the United States between 2015 and 2016, 12.6% of Americans reported past year use annually, and 17.7% of use overall was misuse without a prescription and that was sourced from a friend or relative. Among those ≥ 50 years old, BZDs were more likely to be used more often than prescribed to facilitate sleep. ⁶
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes. In the United States between 2015 and 2016, 12.6% of Americans reported past year use annually, and 17.7% of use overall was misuse without a prescription and that was sourced from a friend or relative. Among those ≥ 50 years old, BZDs were more likely to be used more often than prescribed to facilitate sleep. ⁶
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes.
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. The estimated annual costs of insomnia in the United States range between \$30 and \$107 billion. ⁴ Expenditures for BZDs in Medicaid beneficiaries were \$171.1 million in 2009. ⁵
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	We found two SRs addressing the scope of KQ1, in insomnia ⁹ and panic disorder ¹⁰ populations, respectively, and one in current BZRA users addressing KQ 2.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. The nominator reports inconsistencies between guidelines.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes. Guidelines recommend that BZRAs should be used in the lowest possible duration (1-2 weeks for insomnia, and 2-4 weeks for anxiety), but they are often used continuously at a low steady dose longer term. ¹²
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review	<i>Size/scope of review:</i> We did not find any studies out of a sample of 200 for the BZRA-naïve population of KQ 2.

- Newly available evidence (particularly for updates or new technologies)	
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Abbreviations: AHRQ=Agency for Healthcare Research and Quality; BZD=benzodiazepines; BZRA=benzodiazepine receptor agonist; KQ=key question; SR=systematic review.