Diazepam

Section: 24. Medicines for mental and behavioural disorders > 24.3. Medicines for anxiety disorders

ATC codes: N05BA01

Indication	Anxiety ICD11 code: MB24.3
INN	Diazepam
Medicine type	Chemical agent
List type	Core
Additional notes	For short-term emergency management of acute and severe anxiety symptoms only
Formulations	**Oral > Solid:** 5 mg (scored) ; 2 mg (scored)
EML status history	First added in 1977 (TRS 615) Changed in 1979 (TRS 641) Changed in 1991 (TRS 825) Changed in 1993 (TRS 850) Changed in 2007 (TRS 950) Changed in 2021 (TRS 1035) Changed in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	lorazepam (ATC codes: N05BA06)
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Diazepam
DrugBank	Diazepam

Expert Committee recommendation

The Expert Committee noted that the long-term use of benzodiazepines in the treatment of anxiety disorders was known to be associated with considerable harms in terms of dependence and addiction potential. With short-term use, these risks were greatly reduced. The Committee noted that the updated WHO mhGAP guidelines will include a recommendation limiting the use of benzodiazepines to short-term use (3–7 days) for the emergency management of acute and severe anxiety symptoms only. The Expert Committee therefore recommended the addition of a note to the listing of diazepam for use in anxiety disorders stating that it is only for short-term emergency management of acute and severe anxiety symptoms, as the balance of benefits and risks of diazepam use under these circumstances is favourable. The Expert Committee also accepted the rationale applied by the applicants in selecting lorazepam as the only therapeutic alternative to diazepam for short-term treatment of acute and severe anxiety and recommended that lorazepam be specified as the only therapeutic alternative under the square box listing for diazepam for this indication.

Background

Diazepam, with an unrestricted square box, has been included on the EML since the first list was published in

1977. At its meeting in 2021, the Expert Committee considered a review of square box listings on the EML and EMLc and recommended that all square box listings be qualified to explicitly indicate the recommended therapeutic alternatives. The Committee requested that the therapeutic alternatives for diazepam for use in the treatment of anxiety disorders be reviewed and updated in 2023 (1).

Public health relevance

Anxiety disorders are prevalent and disabling conditions that cause excessive fear, worry and avoidance of threats in the environment. They have a high incidence, early age at onset and a tendency to relapse for a long time (2–4). Guidelines recommend selective serotonin reuptake inhibitors (SSRIs) as the first-choice pharmacological treatment, but benzodiazepines are still commonly used due to their rapid onset of action, perceived effectiveness and favourable side-effects profile in the short term (5–8). Benzodiazepines are classified, under the United Nations Convention of Psychotropic Substances, as schedule IV substances and have a high potential for abuse with addictive potential (9). In 2020 in the United States, 4.8 million individuals misused or abused prescription benzodiazepines (10). In Finland, a population-based cohort study of almost 130 000 new benzodiazepine users found that 39.4% (51 099) of the continuous benzodiazepine users became long-term users (11). Long-term use of benzodiazepines can lead to adverse effects, especially in older individuals, such as cognitive and psychomotor impairments, and increased risk of falls, fractures and even death in many age ranges (12–18). Factors associated with long-term benzodiazepine use include sex, comorbid conditions, older age, lower income, psychiatric comorbidities, substance abuse and poorer health status (11,19–21). Concerns about tolerance and the development of physical dependence have been associated with benzodiazepines for more than 50 years (22,23). Physical dependence can occur with regular use for several days or weeks, leading to withdrawal symptoms when the medication is tapered or reduced (5). Discontinuation of long-term benzodiazepine use is challenging, with only a small percentage of users (13%) able to successfully discontinue within a year (24–26). Benzodiazepine use is associated with a high risk of re-initiation after discontinuation, and abrupt withdrawal or rapid dose reduction can result in life-threatening withdrawal reactions including seizures (23,27). Concomitant use of benzodiazepines and opioids is a major risk factor for drug-related deaths (28), and benzodiazepines, along with cannabis, are among the most prevalent psychoactive substances used by vehicle drivers and their use can impair driving ability including judgement and reaction time, thus increasing the risk of road traffic crashes especially when combined with alcohol (28–30). In September 2020, the United States Food and Drug Administration updated the safety warnings and labelling for all benzodiazepines, highlighting the risks of abuse, misuse, addiction, physical dependence and withdrawal reactions (31).

Benefits

There is consensus among studies that benzodiazepines are generally more effective than placebo in treatment of panic disorders, with no significant differences in efficacy observed between different benzodiazepines (32). Two meta-analyses-compared the effectiveness of psychological and pharmacological treatments (33), and the effect of antidepressants and benzodiazepines versus placebo (34) in the treatment of panic disorders. Both studies showed superiority of benzodiazepines over a placebo in adults. These findings are supported by the results of a 2019 Cochrane systematic review, which found that benzodiazepines had a higher response rate (risk ratio (RR) 1.65, 95% confidence interval (CI) 1.39 to 1.96) and lower drop-out rate (RR 0.50, 95% CI 0.39 to 0.64) compared with placebo (35). Similar results were also found for generalized anxiety disorder (36), social anxiety disorder (37,38) and specific phobias (39,40). Notably, these studies primarily focused on short-term efficacy and did not assess long-term efficacy or the risks of dependency and withdrawal symptoms. A 2022 network meta-analysis of 154 randomized controlled trials (40 089 participants) estimated the comparative effectiveness of pharmacological treatments for acute and long-term treatment of adults with insomnia disorder (41). The study included an analysis of the comparative efficacy of benzodiazepines, grouping them according to half-life (short-, intermediate- and long-acting). No significant differences were found in efficacy for acute treatment of insomnia among the three groups of benzodiazepines. This finding indirectly supports the notion that, when administered at equivalent dosages, all benzodiazepines have a similar beneficial effect on symptoms, noting that the outcome assessed in this study was the resolution of insomnia rather than anxiety symptoms.

Harms

The harms associated with benzodiazepines are well known and well established. Benzodiazepines have similar toxicity profiles and, with some exceptions, abuse, misuse and dependency potential. Common short-time adverse effects include drowsiness, confusion, dizziness, somnolence, fatigue, weakness, memory impairment, impaired coordination and psychomotor retardation. A paradoxical increase in anxiety or disinhibition and delirium may particularly affect elderly patients. Long-term adverse effects include cognitive impairment, increased risk of falls, increased risk of vehicle crashes, depression and emotional blunting. Symptoms of overdose include extreme sedation or drowsiness, reduced respiration rate, confusion and difficulty thinking, slurred speech, loss of muscle control, and coma. Overdose may be fatal if used in combination with alcohol or opioids. Benzodiazepine dependence tends to be more prevalent in populations that already have a history of substance abuse. Studies have shown that about 11% to 15% of adults have used benzodiazepines at least once in the past year. However, only around 1% to 2% have taken benzodiazepines daily for a period of 12 months or more (42). In specific settings, such as psychiatric treatment facilities and among populations struggling with substance abuse, the rates of benzodiazepine use, abuse and dependence are significantly higher than the general population (43,44). The development of physical dependence on benzodiazepines can be predicted to some extent and is related to the total exposure, determined by the dose and duration of treatment. 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 1 month of daily use (45). The incidence of benzodiazepine overdose is influenced by the availability of the medicines (46,47), with the most commonly available benzodiazepines most prone to abuse. In terms of addictive potential, diazepam and lorazepam are not more dangerous than other benzodiazepines. Benzodiazepines with greater addictive potential include flunitrazepam, temazepam and alprazolam. Flunitrazepam is illegal in the United States (48), temazepam is banned in Sweden (5) and alprazolam and flunitrazepam are scheduled as controlled drugs in Australia (49).

Cost / cost effectiveness

The availability and cost of benzodiazepines vary substantially among countries and across public and private sectors. There are no comparative cost–effectiveness studies of single benzodiazepines. Evidence suggests that the use of benzodiazepines may be associated with unnecessary medicine, dispensing and consultation costs resulting from misuse and unnecessary prescribing. A study in the United Kingdom estimated that 67–72% of the total costs associated with benzodiazepines were unnecessary. Over a 3-year period (April 2015–March 2018), the estimated unnecessary costs ranged from about £115.6 million to £129.9 million, with an annual mean unnecessary cost of about £38.5 million to £43.3 million (51). In adults with generalized anxiety disorder, long-term use of benzodiazepines has been shown to significantly increase health care costs. A retrospective cohort study in the United States involving 866 adults found that mean total health care costs increased by US$ 2334 after the start of a long-term (> 90 days) course of benzodiazepine. The costs associated with benzodiazepine use primarily stemmed from accident-related encounters (e.g. treatment of fractures) and care received for other reasons possibly related to benzodiazepine use, such as sedation and dizziness (52). A cost–utility analysis assessed the economic impact of potentially inappropriate prescribing and related adverse events in adults aged 65 years and older. Inappropriate prescribing of benzodiazepines had the largest reduction in quality-adjusted life years (QALYs) and incurred greater incremental costs compared with other medications subject to potentially inappropriate prescribing, such as non-steroidal anti-inflammatory drugs and proton-pump inhibitors. The reduction in QALYs was estimated to be –0.07 QALY, while reduction in the incremental cost was €3470 (53). These findings demonstrate the financial consequences associated with unnecessary use and inappropriate prescribing of benzodiazepines, underscoring the importance of judicious and evidence-based practices in their use.

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders include a strong recommendation that benzodiazepines not be used for the treatment of adults with

generalized anxiety and/or panic disorder. However, for the emergency management of acute and severe anxiety symptoms, benzodiazepines may be considered only as a short-term measure (3–7 days maximum) measure (low certainty of evidence) (50).

Availability

Both diazepam and lorazepam are available globally in originator and generic brands.

Other considerations

The application proposed including lorazepam as an alternative to diazepam because it complements diazepam pharmacokinetically as well as for their therapeutic indications. Diazepam has a long half-life (20–80 hours), while lorazepam has a short half-life (10–20 hours). Diazepam is a medium-potency agent, indicated for milder forms of anxiety, while lorazepam is a high-potency agent, indicated for anxiety surges during panic attacks (54). Although concerns exist about the potential for abuse, misuse and dependence with all benzodiazepines, specific benzodiazepines such as alprazolam, flunitrazepam and temazepam have the higher risks. Thus, these agents were not proposed as therapeutic alternatives to diazepam.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2021 (including the 22nd WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2021 (WHO Technical Report Series, No. 1035; https://apps.who.int/iris/handle/10665/351172, accessed 6 October 2023).
2. Craske MG, Rauch SL, Ursano R, Prenoveau J, Pine DS, Zinbarg RE. What is an anxiety disorder? Depress Anxiety. 2009;26(12):1066–85.
3. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci. 2015;17(3):327–35.
4. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204–22.
5. Lader M. Benzodiazepines revisited--will we ever learn? Addiction. 2011;106(12):2086–109.
6. Andrews G, Bell C, Boyce P, Gale C, Lampe L, Marwat O, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Aust N Z J Psychiatry. 2018;52(12):1109–72.
7. Generalised anxiety disorder and panic disorder in adults: management. Clinical guideline [CG113]. London: National Institute for Health and Care Excellence; 2020 (https://www.nice.org.uk/guidance/cg113, accessed 6 October 2023).
8. Cloos JM, Ferreira V. Current use of benzodiazepines in anxiety disorders. Curr Opin Psychiatry. 2009;22(1):90–5.
9. Convention on psychotropic substances, 1971. Vienna: United Nations; 1971 (https://www.unodc.org/pdf/convention_1971_en.pdf, accessed 6 October 2023).
10. Key substance use and mental health indicators in the United States: results from the 2020 National Survey on Drug Use and Health. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2021 (https://www.samhsa.gov/data/sites/default/files/reports/rpt35325/NSDUHFFRPDFWHTMLFiles2020/2020NSDUHFFR1PDFW102121.pdf, accesssed 6 October 2023).
11. Taipale H, Särkilä H, Tanskanen A, Kurko T, Taiminen T, Tiihonen J, et al. Incidence of and characteristics associated with long-term benzodiazepine use in Finland. JAMA Netw Open. 2020;3(10):e2019029.
12. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. Eur Psychiatry. 2013;28(1):7–20.
13. Lader M. Benzodiazepine harm: how can it be reduced? Br J Clin Pharmacol. 2014;77(2):295–301.
14. Seppala LJ, van de Glind EMM, Daams JG, Ploegmakers KJ, de Vries M, Wermelink A, et al. Fall-risk-increasing drugs: a systematic review and meta-analysis: III. Others. J Am Med Dir Assoc. 2018;19(4):372.e1–e8.
15. Xing D, Ma XL, Ma JX, Wang J, Yang Y, Chen Y. Association between use of benzodiazepines and risk of fractures: a meta-analysis. Osteoporos Int. 2014;25(1):105–20.
16. Donnelly K, Bracchi R, Hewitt J, Routledge PA, Carter B. Benzodiazepines, Z-drugs and the risk of hip fracture: a systematic review and meta-analysis. PLoS One. 2017;12(4):e0174730.
17. Saarelainen L, Tolppanen AM, Koponen M, Tanskanen A, Tiihonen J, Hartikainen S, et al. Risk of death associated with new benzodiazepine use among persons with Alzheimer disease: a matched cohort study. Int J Geriatr Psychiatry. 2018;33(4):583–90.
18. Parsaik AK, Mascarenhas SS, Khosh-Chashm D, Hashmi A, John V, Okusaga O, et al. Mortality associated with anxiolytic and hypnotic drugs: a systematic review and meta-analysis. Aust N Z J Psychiatry. 2016;50(6):520–33.
19. Kurko TA, Saastamoinen LK, Tähkäpää S, Tuulio-Henriksson A, Taiminen T, Tiihonen J, et al. Long-term use of benzodiazepines: definitions, prevalence and usage patterns – a systematic review of register-based studies. Eur Psychiatry. 2015;30(8):1037–47.
20. Cunningham CM, Hanley GE, Morgan S. Patterns in the use of benzodiazepines in British Columbia: examining the impact of increasing research and guideline cautions against long-term use. Health Policy. 2010;97(2–3):122–9.
21. Sidorchuk A, Isomura K, Molero Y, Hellner C, Lichtenstein P, Chang Z, et al. Benzodiazepine prescribing for children, adolescents, and young adults from 2006 through 2013: a total population register-linkage study. PLoS Med. 2018;15(8):e1002635.

22. Systematic review of the benzodiazepines. Guidelines for data sheets on diazepam, chlordiazepoxide, medazepam, clorazepate, lorazepam, oxazepam, temazepam, triazolam, nitrazepam, and flurazepam. Committee on the Review of Medicines. Br Med J. 1980;280(6218):910–2.
23. Hollister LE, Motzenbecker FP, Degan RO. Withdrawal reactions from chlordiazepoxide ("Librium"). Psychopharmacologia. 1961;2:63–8.
24. Dell'Osso B, Albert U, Atti AR, Carmassi C, Carrà G, Cosci F, et al. Bridging the gap between education and appropriate use of benzodiazepines in psychiatric clinical practice. Neuropsychiatr Dis Treat. 2015;11:1885–909.
25. Brandt J, Leong C. Benzodiazepines and Z-drugs: an updated review of major adverse outcomes reported on in epidemiologic research. Drugs R D. 2017;17(4):493–507.
26. Gerlach LB, Strominger J, Kim HM, Maust DT. Discontinuation of chronic benzodiazepine use among adults in the United States. J Gen Intern Med. 2019;34(9):1833–40.
27. Voshaar RC, Gorgels WJ, Mol AJ, van Balkom AJ, Mulder J, van de Lisdonk EH, et al. Predictors of long-term benzodiazepine abstinence in participants of a randomized controlled benzodiazepine withdrawal program. Can J Psychiatry. 2006;51(7):445–52.
28. Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996–2013. Am J Public Health. 2016;106(4):686–8.
29. Joint Formulary Committee. British national formulary 83. London: BMJ Publishing and the Royal Pharmaceutical Society; 2022.
30. European Monitoring Centre for Drugs and Drug Addiction. Selected issue – drugs and driving. 2007. Luxembourg: Publications Office of the European Union; 2007.
31. Integrated drug utilization, epidemiology and pharmacovigilance review: benzodiazepine use, misuse, abuse, dependence, withdrawal, morbidity, and mortality. Silver Spring, MD: Food and Drug Administration; 2020.
32. Moylan S, Staples J, Ward SA, Rogerson J, Stein DJ, Berk M. The efficacy and safety of alprazolam versus other benzodiazepines in the treatment of panic disorder. J Clin Psychopharmacol. 2011;31(5):647–52.
33. Clum GA, Clum GA, Surls R. A meta-analysis of treatments for panic disorder. J Consult Clin Psychol. 1993;61(2):317–26.
34. Wilkinson G, Balestrieri M, Ruggeri M, Bellantuono C. Meta-analysis of double-blind placebo-controlled trials of antidepressants and benzodiazepines for patients with panic disorders. Psychol Med. 1991;21(4):991–8.
35. Breilmann J, Girlanda F, Guaiana G, Barbui C, Cipriani A, Castellazzi M, et al. Benzodiazepines versus placebo for panic disorder in adults. Cochrane Database Syst Rev. 2019;3(3):CD010677.
36. Martin JL, Sainz-Pardo M, Furukawa TA, Martín-Sánchez E, Seoane T, Galán C. Benzodiazepines in generalized anxiety disorder: heterogeneity of outcomes based on a systematic review and meta-analysis of clinical trials. J Psychopharmacol. 2007;21(7):774–82.
37. Davidson JR, Potts N, Richichi E, Krishnan R, Ford SM, Smith R, et al. Treatment of social phobia with clonazepam and placebo. J Clin Psychopharmacol. 1993;13(6):423–8.
38. Munjack DJ, Baltazar PL, Bohn PB, Cabe DD, Appleton AA. Clonazepam in the treatment of social phobia: a pilot study. J Clin Psychiatry. 1990;51(Suppl):35–40; discussion 50–3.
39. Wilhelm FH, Roth WT. Acute and delayed effects of alprazolam on flight phobics during exposure. Behav Res Ther. 1997;35(9):831–41.
40. Roy-Byrne PP, Cowley DS. Pharmacological treatments for panic disorder, generalized anxiety disorder, specific phobia, and social anxiety disorder. In: Nathan PE, Gorman JM, editors. A guide to treatments that work. Third edition. New York, NY: Oxford University Press; 2007:395.
41. De Crescenzo F, D'Alò GL, Ostinelli EG, Ciabattini M, Di Franco V, Watanabe N, 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;400(10347):170–84.
42. Salzman C. The APA Task Force report on benzodiazepine dependence, toxicity, and abuse. Am J Psychiatry. 1991;148(2):151–2.
43. Ciraulo DA, Sands BF, Shader RI. Critical review of liability for benzodiazepine abuse among alcoholics. Am J Psychiatry. 1988;145(12):1501–6.
44. Busto UE, Romach MK, Sellers EM. Multiple drug use and psychiatric comorbidity in patients admitted to the hospital with severe benzodiazepine dependence. J Clin Psychopharmacol. 1996;16(1):51–7.
45. Johnson B, Streltzer J. Risks associated with long-term benzodiazepine use. Am Fam Physician. 2013;88(4):224–6.
46. Kaufmann CN, Spira AP, Alexander GC, Rutkow L, Mojtabai R. Emergency department visits involving benzodiazepines and non-benzodiazepine receptor agonists. Am J Emerg Med. 2017;35(10):1414–9.
47. Soyka M. Treatment of benzodiazepine dependence. N Engl J Med. 2017;376(12):1147–57.
48. Rohypnol fast facts, questions and answers [internet]. Washington, DC: US Department of Justice, National Drug Intelligence Center; 2003 (https://www.justice.gov/archive/ndic/pubs6/6074/index.htm, accessed 6 October 2023).
49. Therapeutic goods (poisons standard—October 2023) Instrument 2023 [internet]. Canberra: Australian Government, Federal Register of Legislation; 2023 (https://www.legislation.gov.au/Details/F2023L01294, accessed 6 October 2023).
50. Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders. Third edition. Geneva: World Health Organization; 2023 (https://iris.who.int/handle/10665/374250, accessed 21 November 2023).
51. Davies J, Cooper RE, Moncrieff J, Montagu L, Rae T, Parhi M. The costs incurred by the NHS in England due to the unnecessary prescribing of dependency-forming medications. Addict Behav. 2022;125:107143.
52. Berger A, Edelsberg J, Treglia M, Alvir JM, Oster G. Change in healthcare utilization and costs following initiation of benzodiazepine therapy for long-term treatment of generalized anxiety disorder: a retrospective cohort study. BMC Psychiatry. 2012;12:177.
53. Moriarty F, Cahir C, Bennett K, Fahey T. Economic impact of potentially inappropriate prescribing and related adverse events in older people: a cost-utility analysis using Markov models. BMJ Open. 2019;9(1):e021832.
54. Chouinard G. Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. J Clin Psychiatry. 2004;65(Suppl 5):7–12.

