Therapeutic Reviews

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Benzodiazepines AHFS 28:24.08

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Benzodiazepines are useful in the management of various symptoms encountered in palliative care. Tolerance and dependence are unlikely to be a problem when used for ≤4 weeks. However, other undesirable effects include drowsiness, falls, and memory and cognitive impairment. Thus, appropriate caution and monitoring is required, particularly for those at greater risk, e.g., the elderly and frail patients.

Indications: Authorized indications vary between products; consult the manufacturers' PIs for details; they include insomnia; anxiety and panic disorder; seizures; myoclonus; skeletal muscle spasm; alcohol withdrawal. Off-label indications include: †drug-induced movement disorders; †restless legs syndrome; †acute psychotic agitation; †terminal agitation; †neuropathic pain; †nausea and vomiting; †intractable pruritus; †intractable hiccup.

Contraindications: Unless in the imminently dying: acute severe pulmonary insufficiency, untreated sleep apnea syndrome, severe liver disease, myasthenia gravis. Also see individual PIs.

Pharmacology

GABA is the major inhibitory neurotransmitter of the nervous system. Several drug classes enhance its action (GABAmimetics):

- $GABA_A$ modulators: benzodiazepines, non-benzodiazepine hypnotics ('Z' drugs, e.g., zopiclone), barbiturates, some general anesthetics (e.g., propofol), alcohol
- $GABA_B$ agonists: baclofen
- inhibitors of GABA transaminase (e.g., vigabatrin) or re-uptake (e.g., tiagibine).[1]

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The $GABA_A$ receptor is a chloride channel formed by 5 subunits comprising varying subtypes (Fig. 1) $GABA_A$ modulators bind to sites distinct from GABA itself (allosteric modulation), increasing the receptor's affinity for GABA (benzodiazepines) or prolonging channel opening (barbiturates).[2] The α subunit of the $GABA_A$ receptor, of which there are six subtypes, is the predominant determinant of benzodiazepine affinity and function (Table 1). In an attempt to improve efficacy and/or tolerability, more selective α-modulators are under investigation, e.g., α2-selective non-sedating anxiolytics.[3]

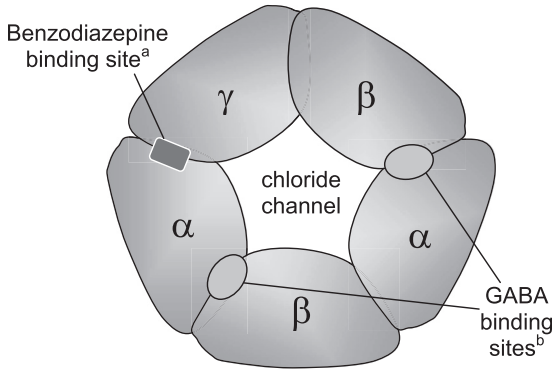

Fig. 1. Structure of the $GABA_A$ receptor.
a. the binding sites for barbiturates, ethanol, neurosteroids and other allosteric modulators are less well characterized
b. the central chloride channel is opened by the concurrent binding of 2 GABA molecules.

Table 1
$GABA_A$ α-subunit Subtypes and Relative Activity of Selected GABAmimetics[3-8]

Alpha Subunit Subtype Function	1 Sleep Anti-epilepsis[b]	2 Anxiolysis Anti-epilepsis[b]	3 Anti-epilepsis[b]	4[a] Anti-epilepsis[b]	5 Amnesia	6[a]
Clonazepam	++	++	++	−		−
Diazepam	++	++	++	−	++	−
Flunitrazepam	++	++	++	−	++	−
Midazolam	++		++	−	++	−
Zaleplon[c]	++	++/+	++/+		++/+	
Zolpidem[c]	++	++/+	++/+	−	−	−
Zopiclone	++	++	−/+[c]	−	+	−
Pentobarbital	++	++	++	++	++	
Ethanol[d]	+	+	+	++	+	

Activity: ++ high, + low, − negligible or none; blank = no data.
[a]Benzodiazepines do not bind to α4- and α6-subunits, or to receptors lacking α and γ subunits (benzodiazepine-insensitive $GABA_A$ receptors).
[b]Relative importance of subunits varies with different seizure models.
[c]α Subunit affinity varies with different β and γ subunit configurations. Prior to cloning, $GABA_A$ classifications encompassed more than one subunit configuration which may account for earlier conflicting affinity data.
[d]Tonic α4(δ) mediated inhibition predominates at lower doses whereas synaptic (α 1, 2 and 3) effects are responsible for severe intoxication. Ethanol also enhances release of GABA and GABAmimetic neurosteroids.

The sedative effects of benzodiazepines (and Z-drugs) probably result from the inhibition of the wakefulness-promoting system.[9,10] Their anxiolytic effects result from α2-$GABA_A$ receptor agonism in the "fear circuits" which are co-ordinated by the amygdala.[11]

Although GABA *antagonists* might be expected to improve wakefulness or memory, the use of non-selective $GABA_A$ antagonists is precluded by anxiogenic and pro-seizure properties. However, the memory-enhancing properties of α5-selective inverse agonists are being investigated. Endogenous ligands for the benzodiazepine binding site include peptide and neurosteroid molecules, but their physiological function is not yet understood.

Most benzodiazepines are well absorbed, widely distributed and metabolized before being eliminated. Their receptor profiles are similar (Table 1) but their potency and half-lives differ (Table 2). Their varied metabolic pathways affect their pharmacogenetic profiles and drug interactions (see individual Prescribing Information for more details). Lorazepam is sometimes given SL, generally when a rapid onset of effect is required and/or the patient cannot reliably swallow tablets. However, ease of dissolution varies between brands and probably explains why one pharmacokinetic study suggested more rapid absorption SL than PO, but others found no difference.[12-15] Thus, the specific SL product should be used (Canada, but not USA, UK), or the most soluble PO alternative. Use of lorazepam 2mg/mL solution is another option in the USA (not UK), but is more expensive.

Table 2
Pharmacokinetics of Selected Benzodiazepines and Related Drugs; PO Unless Stated Otherwise.[16-20]

Drug	Bioavailability PO (%)	Tmax (h)	Plasma Half-life (h)	Metabolism
Alprazolam	≥90[a]	1–2	12–15	CYP3A4
Clonazepam	>80	1–4	20–40	Multiple non-P450 pathways[b]
Clobazam	85	0.5–4	35; (80)[b]	CYP3A4[b]; metabolite inactivated by CYP2C19
Diazepam	>90 65–85 (PR)	0.5–1.5 ≤0.5 (PR)	25–50; (≤200)[b]	Multiple P450 pathways[b]
Lorazepam	90	2.5 2.5 (SL)	10–20	Non-P450 glucuronidation
Midazolam	40 95 (SC) 85 (Buccal)	0.5–1 0.5 (SC) ≤0.5 (Buccal)	1–4[c]; (1)[b]	CYP3A4[b]
Oxazepam	≥90[a]	1–5	6–20	Non-P450 glucuronidation
Temazepam	≥90[a]	1	8–15	Non-P450 glucuronidation
Zaleplon	30[d]	1.5	1	CYP3A4 and non-P450 oxidation
Zolpidem	70	1.5	2	CYP3A4 and CYP1A2
Zopiclone	75	1.5	3.5	CYP3A4[b]

[a]Estimated.
[b]Active metabolite(s).
[c]Up to 24h when given by CIVI in critical care.
[d]Well absorbed but undergoes extensive first pass hepatic metabolism.

Cautions

Benzodiazepines with long half-lives accumulate when given repeatedly and undesirable effects may manifest only after several days or weeks. Caution is required in mild–moderate hepatic impairment and renal impairment. Because their central depressant effect can depress respiration, caution is required in chronic respiratory disease.

Benzodiazepines can cause physical and psychological dependence. Patients with a history of substance abuse should be monitored closely. If long-term treatment is discontinued, taper gradually to avoid withdrawal symptoms, e.g., by one-eighth of the daily dose every 2 weeks. Peak-trough variability can be sufficient to cause withdrawal symptoms when tapering short-acting benzodiazepines; consider switching to an alternative with a longer half-life.

Benzodiazepines are generally safer in overdose than barbiturates and tricyclic antidepressants. However, fatal iatrogenic overdoses of midazolam have occurred. Thus, in the USA, prescribers of midazolam may be required to have additional accreditation in conscious sedation; in the UK, regulators recommend that flumazenil is available for emergency use wherever midazolam is used clinically.[21]

Drug Interactions

For full list, see manufacturer's Prescribing Information

Most clinically relevant interactions arise from hepatic enzyme induction or inhibition or additive effects with other CNS depressants, e.g., alcohol, opioids.

The metabolism of many benzodiazepines is mostly CYP3A4 dependent (Table 2) and plasma concentrations may be decreased or increased to a clinically relevant degree by CYP3A4 inducers (e.g., carbamazepine) or inhibitors (e.g., ketoconazole, erythromycin) respectively. For example, plasma levels of midazolam can be 8 times higher following the addition of a CYP3A4 inhibitor.[22]

Undesirable Effects

For full list, see manufacturer's Prescribing Information

Dose-dependent drowsiness, impaired psychomotor skills (e.g., impaired driving ability), cognitive impairment, hypotonia (manifesting as unsteadiness/ataxia) with an increased (almost double) risk of femoral fracture in the elderly.[23]

Paradoxical arousal, agitation and aggression can occur in <10%; risk factors include high-trait anxiety, borderline personality disorder and alcohol misuse.[24-26]

Less commonly, complex actions while apparently asleep (e.g., driving, eating, cooking, conversations) occur both with benzodiazepines and Z-drugs.[27]

The incidence of dementia is ~50% higher among users of benzodiazepines.[28] This may reflect their use for the prodromal sleep disturbance and anxiety which commonly precedes a diagnosis of dementia.[29,30] Neither a causal link nor a persistent risk beyond cessation of benzodiazepines has been established.

Use of Benzodiazepines in Palliative Care

Choice of benzodiazepine depends on several factors, including availability, route of administration, half-life and cost. In the USA, the main benzodiazepines used in palliative care include clonazepam, diazepam, lorazepam, midazolam and temazepam. Alprazolam is also in common general use, driven, in part, by the previously high cost of lorazepam. However, a large price differential no longer exists. It has been suggested that compared with other benzodiazepines, alprazolam is relatively more toxic in overdose,[31] leading some clinicians to advise against its use.

Insomnia

Initial treatment includes:

- correcting contributory factors if possible:
  - ➢ pain
  - ➢ delirium
  - ➢ depression
  - ➢ obstructive sleep apnea
- non-drug measures.[32-36]

Where drug treatment is required, use a short-half-life benzodiazepine or a Z-drug, ideally for <4 weeks; their efficacy is comparable:

- midazolam (half-life 1−4h) 2.5−5mg PO (not UK) at bedtime *or*
- zopiclone (half-life 3.5h) 7.5mg PO at bedtime (3.75mg initially if elderly or frail) *or*
- temazepam (half-life 8−15h) 10−30mg PO at bedtime.

Indirect comparisons find fewer (mostly minor) undesirable effects with Z-drugs.[37] This may reflect their shorter half-lives (except for midazolam). The clinical relevance of their greater α-subunit subtype selectivity (see above) is questionable because many undesirable effects are direct consequences of sedation.

A meta-analysis confirmed that, in people >60 years of age, benzodiazepines and Z-drugs had an NNT of 13 but an NNH of 6.[38] The undesirable effects were cognitive impairment, day-time drowsiness, ataxia and falls. Even low doses of short half-life benzodiazepines increase the risk of falls.[39] Alternatives include sedating antidepressants (e.g., doxepin, mirtazapine, trazodone)[40] and melatonin.[41,42]

Anxiety and Panic Disorder

The efficacy of cognitive behavioral and drug therapy is comparable.[43] Drug treatment is tailored to the likely duration of use:

- benzodiazepine, if prognosis is <2−4 weeks, e.g., diazepam 2−10mg at bedtime, lorazepam 0.5−1mg b.i.d.
- SSRI (± a benzodiazepine initially), if prognosis is >2−4 weeks.

Pregabalin also acts quickly but it is generally reserved for patients not responding to antidepressants. Supporting trials are mostly confined to generalized anxiety disorder and response rates appear lower than for SSRIs and benzodiazepines.[44,45]

Depression

Benzodiazepines lack an antidepressant effect and are not routinely indicated in the management of depression.[46] However, their initial short-term use (<4 weeks) may be helpful when there is associated severe anxiety.

Acute Psychotic Agitation

Lorazepam is as effective as haloperidol 5mg every 30min in initially calming the patient:[47]

- lorazepam 2mg PO/IM every 30min until the patient is settled.

Terminal Agitation

- start with midazolam 2.5−10mg SC p.r.n. and 10mg/24h CSCI
- if necessary, increase both the as needed dose and CSCI until the patient is settled (commonly 10−60mg/24h CSCI, with ≤240mg/24h reported on occasion)
- however, if midazolam is poorly effective, or if >30mg/24h needed, consider adding an antipsychotic (e.g., haloperidol or levomepromazine (not USA))
- if midazolam plus an antipsychotic are poorly effective despite titration, consider switching to phenobarbital or propofol.

Breathlessness

Benzodiazepines do not relieve breathlessness *per se*[48] but anxiolytics do have a role when *anxiety* exacerbates breathlessness. Either a benzodiazepine or an SSRI is used depending on prognosis (see above).

In the last days of life, for patients with distressing breathlessness at rest, the combined use of an opioid with a benzodiazepine is more effective than either alone.[49]

Seizures

Benzodiazepines are first line treatments for acute seizures, including status epilepticus. However, their long-term use is hampered by the development of tolerance; thus they are used only for epilepsy refractory to other measures.

Acute treatment[50]

- lorazepam 4mg IV over 2min *or*
- midazolam 10mg IV over 2min or SC/buccal; the injection can be given buccally in status epilepticus.

If necessary, give two more doses at 10min intervals.[51]

Particularly in children, buccal midazolam has mostly rendered the use of rectal diazepam obsolete.[52]

Chronic treatment refractory to conventional anti-epileptic drugs

- start with clonazepam 500microgram−1mg PO at bedtime
- if necessary, increase by 500microgram every 3−5 days up to 2−4mg, occasionally more
- doses above 2mg can be divided, e.g., 2mg at bedtime and 1mg each morning.

End of life care

- midazolam 10mg SC p.r.n. *and* 20−30mg/24h CSCI.

Alternative SC anti-epileptics include phenobarbital,[53] sodium valproate[54] and levetiracetam.[55]

Myoclonus

Treat the underlying cause if possible:

- drug-related, e.g., opioids, gabapentin or pregabalin: consider dose reduction or switching to an alternative
- metabolic disturbance, e.g., hyponatremia, uremia.

Otherwise, a benzodiazepine should be used, e.g.:

- clonazepam 0.5mg PO at bedtime o*r*
- midazolam 5mg SC stat and 10mg/24h CSCI in moribund patients.

If necessary, give as needed doses and consider increasing the regular dose.

Restless Legs Syndrome

Clonazepam is an option for selected patients with restless legs syndrome when first-line options (e.g., rotigotine, ropinirole) are ineffective or inappropriate. Gabapentin and pregabalin are alternatives. Iron supplementation may be effective in those with iron deficiency.[56,57]

Drug-induced Movement Disorders

Acute movement disorders. Reduce or stop the causal drug if possible. Otherwise, switch to an alternative with a lower risk of extrapyramidal reactions, (e.g., metoclopramide → domperidone, haloperidol → quetiapine).[58] If symptoms are causing distress, give an antimuscarinic, e.g., procyclidine; if latter ineffective or contraindicated, RCTs indicate a *possible* role for benzodiazepines in acute akathisia and dystonia:

- clonazepam 0.5−1mg/24h PO, increased if necessary to 2.5mg/24h[59] *or*
- diazepam 5mg IV.[60]

Tardive dyskinesia. Reduce, stop or switch the causal drug as above and seek specialist advice. No symptomatic treatment has been found consistently effective. Small RCTs have found clonazepam (mean daily dose 5mg) of modest benefit, but diazepam and alprazolam both ineffective.[58,61]

Neuropathic Pain

Clonazepam is reported to improve both cancer-related and non-cancer neuropathic pain.[62-65] Antihyperalgesic properties have been confirmed in healthy volunteers.[66] Its anxiolytic and muscle-relaxant properties and the ability to administer it SC in some countries (not USA, UK), has led to its use in selected palliative care patients despite the absence of supporting RCTs.[67]

Skeletal Muscle Spasm

Benzodiazepines are used for the management of pain due to skeletal muscle spasm, e.g., acute low back pain:[68]

- diazepam 2−5mg PO at bedtime and as required.

If the anticipated duration of use is ≥3−4 weeks, to avoid problems associated with the long-term use of benzodiazepines (see Cautions), some clinicians use baclofen instead. For similar reasons, although benzodiazepines also have been used in the long-term management of spasticity secondary to neurological disorders, generally alternative skeletal muscle relaxants are preferred, e.g., baclofen, tizanidine. However, there is little evidence to support any one approach over another.[69,70]

Parenteral benzodiazepines, e.g., midazolam 10mg/24h CSCI, can be used to relieve muscle spasm and spasticity in the last days of life.

Nausea and Vomiting

Benzodiazepines are effective for chemotherapy-induced[71-73] and postoperative[74] nausea and vomiting:

- lorazepam 0.5mg SL p.r.n. *or*
- midazolam 10−20mg/24h CSCI.

Although a specific role for benzodiazepines in *anticipatory* nausea has been proposed, there is limited evidence to support this over and above their general antiemetic effect. Alternative approaches to anticipatory nausea include relaxation, hypnosis and other psychological approaches.[75,76]

Alcohol Withdrawal

Benzodiazepines reduce withdrawal symptoms, particularly seizures.[77] The choice is as for seizures (see above) with dose and route dependent on severity of withdrawal syndrome.[78,79]

Pruritus

Benzodiazepines are not consistently effective for pruritus.[80-82] Their place, if any, in patients refractory to usual measures[83] is uncertain.

Hiccup

Midazolam is reported to improve hiccup refractory to various other approaches, e.g., metoclopramide, haloperidol, chlorpromazine, simethicone, baclofen, alone or in combination.[84,85]

Switching Between Benzodiazepines

Dose conversion is not straightforward and switching is best avoided when possible. However, when necessary, use the dose equivalence table to provide a starting point (Table 3). Equivalent doses are always approximations, and appropriate caution and monitoring is required. Particularly when switching at a high dose, it is prudent to use, say, a 30−40% lower dose than predicted and to ensure that flumazenil or additional benzodiazepine doses are available for p.r.n. use.

When converting from PO diazepam to SC midazolam, the dose should be halved (e.g. diazepam 5mg PO → midazolam 2.5mg SC).[86,87] However, PO, they are similar in potency because the bio-availability of midazolam is about half that of diazepam (Table 2).

Table 3
Approximate Equivalent PO Anxiolytic-Sedative Doses[88-91]

Drug	Dose (PO)
Alprazolam	0.5mg
Chlordiazepoxide	15mg
Clonazepam	250microgram
Diazepam	5mg
Lorazepam	500microgram
Midazolam	5mg
Nitrazepam	5mg
Oxazepam	15mg
Temazepam	10mg

Abbreviations

†	Off-label use
b.i.d.	Bis in die, twice daily
CNS	Central nervous system
CSCI	Continuous subcutaneous infusion
CYP	Cytochrome P450
GABA	Gamma-aminobutyric acid
IM	Intramuscular
IV	Intravenous
NNH	Number needed to harm
NNT	Number needed to treat
PI	Prescribing information
PO	Per os, by mouth
PR	Per rectum
p.r.n.	Pro re nata, as required
RCT	Randomized controlled trial
SC	Subcutaneous
SL	Sublingual
SSRI	Selective serotonin re-uptake inhibitor

References

1. Howard P, Twycross R, Shuster J, et al. Anti-epileptic drugs. J Pain Symptom Manage 2011;42:788−804.

2. Rudolph U, Mohler H. GABA-based therapeutic approaches: GABAA receptor subtype functions. Curr Opin Pharmacol 2006;6:18−23.

3. Mohler H. The rise of a new GABA pharmacology. Neuropharmacology 2011;60:1042−1049.

4. Graham D, Faure C, Besnard F, Langer SZ. Pharmacological profile of benzodiazepine site ligands with recombinant GABAA receptor subtypes. Eur Neuropsychopharmacol 1996;6:119−125.

5. Pritchett DB, Lüddens H, Seeburg PH. Type I and type II GABAA-benzodiazepine receptors produced in transfected cells. Science 1989;245:1389−1392.

6. Smith AJ, Alder L, Silk J, et al. Effect of alpha subunit on allosteric modulation of ion channel function in stably expressed human recombinant gamma-aminobutyric acid(A) receptors determined using (36) Cl ion flux. Mol Pharmacol 2001;59:1108−1118.

7. Kumar S, Porcu P, Werner DF, et al. The role of GABA(A) receptors in the acute and chronic effects of ethanol: a decade of progress. Psychopharmacology (Berl) 2009;205:529−564.

8. Sanna E, Busonero F, Talani G, et al. Comparison of the effects of zaleplon, zolpidem, and triazolam at

various GABA(A) receptor subtypes. Eur J Pharmacol 2002;451:103–110.

9. Rihel J, Schier AF. Sites of action of sleep and wake drugs: insights from model organisms. Curr Opin Neurobiol 2013;23:831–840.

10. Lazarus M, Chen JF, Urade Y, Huang ZL. Role of the basal ganglia in the control of sleep and wakefulness. Curr Opin Neurobiol 2013;23:780–785.

11. Dias BG, Banerjee SB, Goodman JV, Ressler KJ. Towards new approaches to disorders of fear and anxiety. Curr Opin Neurobiol 2013;23:346–352.

12. Caillé G, Spénard J, Lacasse Y, Brennan J. Pharmacokinetics of two lorazepam formulations, oral and sublingual, after multiple doses. Biopharm Drug Dispos 1983;4:31–42.

13. Greenblatt DJ, Divoll M, Harmatz JS, Shader RI. Pharmacokinetic comparison of sublingual lorazepam with intravenous, intramuscular, and oral lorazepam. J Pharm Sci 1982;71:248–252.

14. Spénard J, Caillé G, de Montigny C, et al. Placebo-controlled comparative study of the anxiolytic activity and of the pharmacokinetics of oral and sublingual lorazepam in generalized anxiety. Biopharm Drug Dispos 1988;9:457–464.

15. Gram-Hansen P, Schultz A. Plasma concentrations following oral and sublingual administration of lorazepam. Int J Clin Pharmacol Ther Toxicol 1988;26:323–324.

16. Riss J, Cloyd J, Gates J, Collins S. Benzodiazepines in epilepsy: pharmacology and pharmacokinetics. Acta Neurol Scand 2008;118:69–86.

17. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. Clin Pharmacokinet 2004;43:227–238.

18. Pecking M, Montestruc F, Marquet P, et al. Absolute bioavailability of midazolam after subcutaneous administration to healthy volunteers. Br J Clin Pharmacol 2002;54:357–362.

19. Scott LJ, Lyseng-Williamson KA, Garnock-Jones KP. Oromucosal midazolam: a guide to its use in paediatric patients with prolonged acute convulsive seizures. CNS Drugs 2012;26:893–897.

20. Beigmohammadi MT, Hanifeh M, Rouini MR, Sheikholeslami B, Mojtahedzadeh M. Pharmacokinetics alterations of midazolam infusion versus bolus administration in mechanically ventilated critically ill patients. Iran J Pharm Res 2013;12:483–488.

21. NPSA (National Patient Safety Agency). Reducing risk of overdose with midazolam injection in adults. Rapid response report 11. 2008. Available from www.nrls.npsa.nhs.uk/resources/?entryid45=59896.

22. Kotlinska-Lemieszek A. Should midazolam drug-drug interactions be of concern to palliative care physicians? Drug Saf 2013;36:789–790.

23. Grad R. Benzodiazepines for insomnia in community-dwelling elderly: a review of benefit and risk. J Fam Pract 1995;41:473–481.

24. Mancuso CE, Tanzi MG, Gabay M. Paradoxical reactions to benzodiazepines: literature review and treatment options. Pharmacotherapy 2004;24:1177–1185.

25. Weinbroum AA, Szold O, Ogorek D, Flaishon R. The midazolam-induced paradox phenomenon is reversible by flumazenil. Epidemiology, patient characteristics and review of the literature. Eur J Anaesthesiol 2001;18:789–797.

26. Saias T, Gallarda T. Paradoxical aggressive reactions to benzodiazepine use: a review. [in French]. Encephale 2008;34:330–336.

27. Dolder CR, Nelson MH. Hypnosedative-induced complex behaviours: incidence, mechanisms and management. CNS Drugs 2008;22:1021–1036.

28. Billioti de Gage S, Bégaud B, Bazin F, et al. Benzodiazepine use and risk of dementia: prospective population based study. BMJ 2012;345:e6231.

29. Bocti C, Roy-Desruisseaux J, Roberge P. Research paper most likely shows that benzodiazpeines are used to treat early symptoms of dementia. [Letter]. BMJ 2012;345:e7986.

30. Coyle-Gilchrist IT, Peck LF, Rowe JB. Research paper does now show casual link between benzodiazepines use and diagnosis of dementia. [Letter]. BMJ 2012;345:e7984.

31. Isbister GK, O'Regan L, Sibbritt D, Whyte IM. Alprazolam is relatively more toxic than other benzodiazepines in overdose. Br J Clin Pharmacol 2004;58:88–95.

32. Morin CM, Culbert JP, Schwartz SM. Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. Am J Psychiatry 1994;151:1172–1180.

33. Murtagh DR, Greenwood KM. Identifying effective psychological treatments for insomnia: a meta-analysis. J Consult Clin Psychol 1995;63:79–89.

34. Smith MT, Perlis ML, Park A, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. Am J Psychiatry 2002;159:5–11.

35. Hugel H, Ellershaw JE, Cook L, Skinner J, Irvine C. The prevalence, key causes and management of insomnia in palliative care patients. J Pain Symptom Manage 2004;27:316–321.

36. Twycross R, Wilcock A, Toller CS. Symptom management in advanced cancer, 4th ed. Nottingham: palliativedrugs.com, 2009:203–204.

37. Buscemi N, Vandermeer B, Friesen C, et al. The efficacy and safety of drug treatments for chronic insomnia

in adults: a meta-analysis of RCTs. J Gen Intern Med 2007;22:1335–1350.

38. Glass J, Lanctôt KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ 2005; 331:1169.

39. Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. Am J Psychiatry 2001;158:892–898.

40. Howard P, Twycross R, Shuster J, Mihalyo M, Wilcock A. Antidepressant drugs. J Pain Symptom Manage 2012;44:763–783.

41. Melatonin. In: Twycross R, Wilcock A, eds. Palliative care formulary, 4th ed Nottingham: palliativedrugs.com, 2011:148–150.

42. Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. J Psychopharmacol 2010;24:1577–1601.

43. Bandelow B, Seidler-Brandler U, Becker A, Wedekind D, Rüther E. Meta-analysis of randomized controlled comparisons of psychopharmacological and psychological treatments for anxiety disorders. World J Biol Psychiatry 2007;8:175–187.

44. Baldwin DS, Anderson IM, Nutt DJ, et al. British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2005; 19:567–596.

45. Baldwin D. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. BMJ 2011;342:1199.

46. Furukawa TA, Streiner DL, Young LT. Antidepressant plus benzodiazepine for major depression. Cochrane Database Syst Rev 2001;CD001026.

47. Foster S, Kessel J, Berman ME, Simpson GM. Efficacy of lorazepam and haloperidol for rapid tranquilization in the psychiatric emergency room setting. Int Clin Psychopharmacol 1997;12:175–179.

48. Simon ST, Higginson IJ, Booth S, Harding R, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database Syst Rev 2010; CD007354.

49. Navigante AH, Cerchietti LC, Castro MA, Lutteral MA, Cabalar ME. Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. J Pain Symptom Manage 2006;31:38–47.

50. Rey E, Tréluyer JM, Pons G. Pharmacokinetic optimization of benzodiazepines therapy for acute seizures. Focus on delivery routes. Clin Pharmacokinet 1999;36: 409–424.

51. British National Formulary. Section 4.8.2 Drugs used in status epilepticus. In: British National Formulary (No. 61). London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2013. Current BNF available from www.bnf.org.

52. McIntyre J, Robertson S, Norris E, et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. Lancet 2005;366:205–210.

53. Twycross R, Wilcock A. Phenobarbital. Palliative care formulary, 4th ed. Nottingham: palliativedrugs.com, 2011:270–274.

54. Twycross R, Wilcock A. Valproate. Palliative care formulary, 4th ed. Nottingham: palliativedrugs.com, 2011: 264–268.

55. López-Saca JM, Vaquero J, Larumbe A, Urdíroz J, Centeno C. Repeated use of subcutaneous levetiracetam in a palliative care patient. [Letter]. J Pain Symptom Manage 2013;45:e7–e8.

56. Aurora RN, Kristo DA, Bista SR, et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults-an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. Sleep 2012;35: 1039–1062.

57. Garcia-Borreguero D, Ferini-Strambi L, Kohnen R, et al. European guidelines on management of restless legs syndrome: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society. Eur J Neurol 2012;19:1385–1396.

58. Twycross R, Wilcock A. Drug-induced movement disorders. Palliative care formulary, 4th ed. Nottingham: palliativedrugs.com, 2011:745–749.

59. Lima AR, Soares-Weiser K, Bacaltchuk J, Barnes TR. Benzodiazepines for neuroleptic-induced acute akathisia. Cochrane Database Syst Rev 2002;CD001950.

60. Gagrat D, Hamilton J, Belmaker RH. Intravenous diazepam in the treatment of neuroleptic-induced acute dystonia and akathisia. Am J Psychiatry 1978;135: 1232–1233.

61. Bhoopathi PS, Soares-Weiser K. Benzodiazepines for neuroleptic-induced tardive dyskinesia. Cochrane Database Syst Rev 2006;CD000205.

62. Hugel H, Ellershaw JE, Dickman A. Clonazepam as an adjuvant analgesic in patients with cancer-related neuropathic pain. J Pain Symptom Manage 2003;26: 1073–1074.

63. Bartusch SL, Sanders BJ, D'Alessio JG, Jernigan JR. Clonazepam for the treatment of lancinating phantom limb pain. Clin J Pain 1996;12:59–62.

64. Bouckoms AJ, Litman RE. Clonazepam in the treatment of neuralgic pain syndrome. Psychosomatics 1985; 26:933–936.

65. Swerdlow M, Cundill J. Anticonvulsant drugs used in the treatment of lancinating pain: a comparison. Anaesthesia 1981;36:1129–1132.

66. Vuilleumier PH, Besson M, Desmeules J, Arendt-Nielsen L, Curatolo M. Evaluation of anti-hyperalgesic and analgesic effects of two benzodiazepines in human experimental pain: a randomized placebo-controlled study. PLoS One 2013;8:e43896.

67. Corrigan R, Derry S, Wiffen PJ, Moore RA. Clonazepam for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2012;CD009486.

68. Chou R, Huffman LH. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med 2007;147: 505–514.

69. Shakespeare DT, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis. Cochrane Database Syst Rev 2003;CD001332.

70. Taricco M, Adone R, Pagliacci C, Telaro E. Pharmacological interventions for spasticity following spinal cord injury. Cochrane Database Syst Rev 2000;CD001131.

71. Bishop JF, Olver IN, Wolf MM, et al. Lorazepam: a randomized, double-blind, crossover study of a new antiemetic in patients receiving cytotoxic chemotherapy and prochlorperazine. J Clin Oncol 1984;2:691–695.

72. Razavi D, Delvaux N, Farvacques C, et al. Prevention of adjustment disorders and anticipatory nausea secondary to adjuvant chemotherapy: a double-blind, placebo-controlled study assessing the usefulness of alprazolam. J Clin Oncol 1993;11:1384–1390.

73. Malik IA, Khan WA, Qazilbash M, et al. Clinical efficacy of lorazepam in prophylaxis of anticipatory, acute, and delayed nausea and vomiting induced by high doses of cisplatin. A prospective randomized trial. Am J Clin Oncol 1995;18:170–175.

74. Di Florio T, Goucke CR. The effect of midazolam on persistent postoperative nausea and vomiting. Anaesth Intensive Care 1999;27:38–40.

75. Mandalà M, Cremonesi M, Rocca A, et al. Midazolam for acute emesis refractory to dexamethasone and granisetron after highly emetogenic chemotherapy: a phase II study. Support Care Cancer 2005;13:375–380.

76. Aapro MS, Molassiotis A, Olver I. Anticipatory nausea and vomiting. Support Care Cancer 2005;13: 117–121.

77. Amato L, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. Cochrane Database Syst Rev 2010;CD005063.

78. Peppers MP. Benzodiazepines for alcohol withdrawal in the elderly and in patients with liver disease. Pharmacotherapy 1996;16:49–57.

79. Chick J. Review: benzodiazepines are more effective than neuroleptics in reducing delirium and seizures in alcohol withdrawal. Evid Based Ment Health 1998;3:11.

80. Hägermark O. Influence of antihistamines, sedatives, and aspirin on experimental itch. Acta Derm Venereol 1973;53:363–368.

81. Muston H, Felix R, Shuster S. Differential effect of hypnotics and anxiolytics on itch and scratch. J Invest Dermatol 1979;72:283.

82. Ebata T, Izumi H, Aizawa H, Kamide R, Niimura M. Effects of nitrazepam on nocturnal scratching in adults with atopic dermatitis: a double-blind placebo-controlled crossover study. Br J Dermatol 1998;138:631–634.

83. Twycross R, Greaves MW, Handwerker H, et al. Itch: scratching more than the surface. QJM 2003;96:7–26.

84. Moro C, Sironi P, Berardi E, Beretta G, Labianca R. Midazolam for long-term treatment of intractable hiccup. [Letter]. J Pain Symptom Manage 2005;29: 221–223.

85. Wilcock A, Twycross R. Midazolam for intractable hiccup. J Pain Symptom Manage 1996;12:59–61.

86. Whitwam JG, Al-Khudhairi D, McCloy RF. Comparison of midazolam and diazepam in doses of comparable potency during gastroscopy. Br J Anaesth 1983;55: 773–777.

87. Cole SG, Brozinsky S, Isenberg JI. Midazolam, a new more potent benzodiazepine, compared with diazepam: a randomized, double-blind study of preendoscopic sedatives. Gastrointest Endosc 1983;29:219–222.

88. British National Formulary. Section 4.1. Hypnotics and anxiolytics, . British National Formulary (No. 61). London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2013. Current BNF available from www.bnf.org.

89. American Society of Health-System Pharmacists (AHFS). Benzodiazepines general statement (pharmacokinetics). AHFS Drug Information 2009 (online edition). Available from www.ahfsdruginformation.com/ (subscription required).

90. Taylor D, Paton C, Kapur S, eds. Benzodiazepines: dependence and detoxification. In: The Maudsley prescribing guidelines in psychiatry, 11th ed Chichester: Wiley-Blackwell, 2012:307–308.

91. Bazire S. Psychotropic drug directory. Cheltenham: Lloyd-Reinhold Communications LLP, 2012:211.