Issues in the Clinical Use of Benzodiazepines: Potency, Withdrawal, and Rebound

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Low and medium potency benzodiazepines were initially introduced for the treatment of insomnia and anxiety. Their therapeutic actions as anxiolytics, sedative hypnotics, anticonvulsants, and muscle relaxants (with their low toxicity) have led to their use as first-line treatments, and they have become one of the most prescribed classes of drugs. Novel therapeutic uses of benzodiazepines were discovered with the introduction of the high-potency benzodiazepines (e.g., alprazolam, clonazepam, and lorazepam). They were found to be effective in treating panic disorder and panic attacks with or without agoraphobia, as add-on therapy to selective serotonin reuptake inhibitors in the treatment of obsessive-compulsive disorder and panic disorders, and as adjunctive therapy in treating patients with acute mania or acute agitation. High-potency benzodiazepines have replaced low and medium potency benzodiazepines in all benzodiazepine clinical indications due to their greater therapeutic effects and rapid onset of action. Differences in distribution, elimination half-life, and rate of absorption are important considerations when choosing a high-potency benzodiazepine. Typically, a benzodiazepine with long distribution and elimination half-lives is preferred. A maximum dose of 2 mg/day of any of the high-potency benzodiazepines when given for more than 1 week is recommended. Although as a class benzodiazepines act rapidly and are well tolerated, their use presents clinical issues such as dependence, rebound anxiety, memory impairment, and discontinuation syndrome.

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Investigations into the role of serotonin in the treatment of psychiatric illness led our Montreal group to the first studies[1–9] of high-potency benzodiazepines in severely ill psychiatric patients and their use in the treatment of mania[10] and panic attacks.[11] Alprazolam, the first high-potency benzodiazepine studied in panic disorder, not only proved effective for anticipatory anxiety, but it also blocked panic attacks and was well tolerated.[12] Before 1982, treatment of patients with panic disorder was limited to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), which are associated with cardiovascular and anticholinergic side effects. Shortly after, we found another high-potency benzodiazepine, clonazepam, a serotonin agonist and anticonvulsant, to be at least as effective as lithium for the treatment of acute mania,[10] and to be as effective as alprazolam in the treatment of panic disorder without the rebound anxiety effect seen with alprazolam.[13] Later, lorazepam, another high-potency benzodiazepine with anticonvulsant properties, was found to be effective as adjunctive treatment in mania and agitation.[14,15] Because different therapeutic indications require benzodiazepines of different potencies, classifying them by low, medium, and high potency became necessary (Table 1).[16–19]

More recently, we found the anticonvulsant agent gabapentin to be efficacious for treating anxiety and related disorders.[20] Through its unique mechanism of action as an anticonvulsant, gabapentin confirms the role of clonazepam as an anticonvulsant in the treatment of panic disorders. Although gabapentin alone is not as effective as clonazepam in treating panic or social phobia,[21,22] as adjunctive therapy it potentiates the anticonvulsant and antipanic effects of clonazepam[20] and may be given as adjunctive treatment when a dose greater than 2 mg/day of a high-potency benzodiazepine is needed.

In the early 1980s, high-potency benzodiazepines were found to be effective treatments for panic and mania (see the article by J. F. Rosenbaum elsewhere in this supplement).[10–13,23–26] The advantages of benzodiazepines over prior agents include a greater therapeutic dose margin between anxiolysis and sedation, rapid onset of action, less risk of dependence, less respiratory depression, and a higher ratio of median lethal dose to median effective dose. The success of benzodiazepines in treating panic and acute agitation led to further success associated with high-potency benzodiazepines. The rapid onset with low toxicity and desirable therapeutic actions of benzodiazepines as anxiolytics, sedatives, anticonvulsants, and muscle relaxants have led to their first successful use as first-line treatments for

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Table 1. Classification of Selected Benzodiazepines

Potency/ Benzodiazepine	Therapeutic Indications	Approximate Dose Equivalence (mg/d)[a]	Recommended Length of Treatment (wk)[b]	Elimination Half-Life of Parent Compound (h)[a]	HPLC Retention Index (relative to diazepam)[c]	Binding Affinity K_i (nM)[d]
Low	Very mild generalized					
Chlordiazepoxide	anxiety or insomnia	10	16	7–30	…	…
Oxazepam[e]		15	16	6–24	0.45	11.53
Temazepam[e,f]		30	5	8–24	…	23.50
Medium	Mild generalized anxiety					
Clorazepate[g]	or insomnia	7.5	16	30–60	…	…
Diazepam[g]		5	16	20–80	1.00	9.57
Desmethyldiazepam		…	…	30–100	0.79	5.58
Estazolam		…	15	10–24	0.39	…
Flurazepam[f,g]		30	4	72	…	…
Prazepam[g]		…	4	30–60	…	…
Quazepam[g]		…	13	15–35	…	…
High	Panic attacks, generalized					
Alprazolam[e]	anxiety disorder, insomnia,	0.5	16	6–20	0.54	4.24
Bromazepam[e]	agitation, mania	3	16	8–19	0.24	…
Clonazepam[g]		0.25	16	5–30	0.28	0.51
Lorazepam[e]		1	16	10–20	0.48	1.64
Triazolam[a,h]		0.25	2	2–5	0.64	0.47

[a]Data from Nelson and Chouinard.[16] [b]Data from AHFS Drug Information.[17] [c]Data from Ochs et al.[18] Higher numbers indicate greater lipid solubility. [d]Data from Greenblatt et al.[19] Higher numbers indicate greater affinity. [e]Short to intermediate half-life (5–24 h). [f]Approved by the U.S. Food and Drug Administration as a hypnotic. [g]Long half-life (≥ 24 h). [h]Ultrashort half-life (< 5 h). Abbreviation: HPLC = high performance liquid chromatography.

anxiety.[13] In the early 1980s, with the introduction of the DSM-III classification, anxiety disorders fell into 3 main categories: generalized anxiety disorder (GAD), panic disorder, and obsessive-compulsive disorder (OCD). New psychiatric indications for high-potency benzodiazepines include panic attacks with and without agoraphobia, acute mania, and acute agitation. Low and medium potency benzodiazepines were not recognized as efficacious for these indications. However, discontinuation symptoms were found to be more frequent with some of the high-potency benzodiazepines with short to intermediate elimination half-lives (see Table 1).

REBOUND ANXIETY AND DISCONTINUATION SYNDROMES

When treatment with benzodiazepines is stopped, patients may experience recurrent, rebound, or new withdrawal symptoms.[13] Recurrent symptoms are a gradual return of the patient's original symptoms with the same rate of intensity as before treatment. Rebound symptoms are a rapid return of the patient's original symptoms but worse than before treatment. Some rebound symptoms may be those for which the agent was prescribed. Thus, when benzodiazepines are abruptly discontinued, anxiety and insomnia are common rebound symptoms. Patients often respond rapidly to the reinstitution of the drug, which may lead to a false sense of efficacy and lead to psychological dependence. Finally, central nervous system (CNS) withdrawal symptoms are new symptoms that were not part of the patient's illness before treatment and are associated with specific CNS classes of drugs (e.g., narcotics, barbiturates, and benzodiazepines).

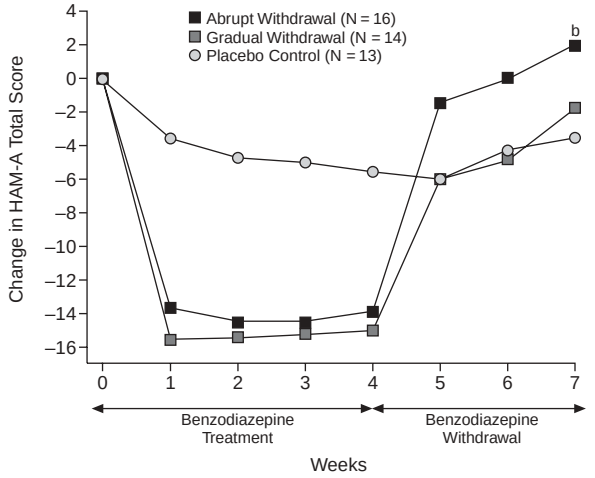
Table 2. Early Termination Related to Rebound Anxiety During Abrupt Withdrawal of Benzodiazepines After Short-Term Administration in 4 Placebo-Controlled Studies (N = 128)[a]

Termination	Placebo	Diazepam	Bromazepam	Lorazepam
Yes, N	1	5	16	12
No, N	49	17	20	7
Total, N	50	22	35	19
Terminated, %[b]	2	23	46	63

[a]Reprinted with permission from Chouinard.[27]
[b]$\chi^2 = 34.89$, df = 3, $p < .001$.

The prevalence of rebound anxiety was found to be greater among patients taking benzodiazepines with short to intermediate half-lives than those taking agents with long elimination half-lives.[27–29] In a review of data from 4 placebo-controlled studies (N = 128), the risk of rebound anxiety during benzodiazepine withdrawal was related to elimination half-life and potency (Table 2).[27] In one of those studies, an 8-week, double-blind, placebo-controlled study[30] of rebound anxiety in 48 patients with GAD (DSM-III criteria from the 1978 draft) who scored ≥ 20 on the Hamilton Rating Scale for Anxiety (HAM-A) at baseline, patients were randomly assigned to bromazepam, diazepam, or placebo. Rebound anxiety was defined as an increase of ≥ 10% from baseline scores on both the HAM-A and the Self-Rating Symptom Scale. At week 4, medication was abruptly withdrawn in half of the patients in each group and gradually withdrawn in the remaining half. Abrupt withdrawal of benzodiazepines resulted in 7 cases of rebound anxiety: 5 (62.5%) of 8 patients in the bromazepam group and 2 (25%) of 8 patients in the diazepam group. Figure 1 shows the rapid return of anxiety symptoms when

Figure 1. Abrupt Versus Gradual Withdrawal of Benzodiazepines in Patients With GAD After 4 Weeks of Treatment[a]



[a]Reprinted with permission from Fontaine et al.[30] [b]Rebound anxiety.
Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety.

Table 3. Minor New Symptoms Occurring During Benzodiazepine Withdrawal in Patients With GAD and in Control Subjects[a]

	Patients Withdrawn Abruptly (N = 16)		Patients Withdrawn Gradually (N = 14)		Controls (N = 13)	
Symptom	N	%	N	%	N	%
Insomnia	10	63[b]	5	36	2	15[b]
Gastric problem	8	50[c]	6	43	2	15[c]
Tremors	8	50	5	36	3	23
Agitation	5	31	6	43[b]	1	8[b]
Fearfulness	5	31	3	21	1	8
Muscle spasms	4	25[c]	2	14	0[c]	...
Sweating	1	6	2	14	1	8
Depression	1	6	1	7	0	...
Memory lapses	1	6	0	...	0	...
Flushes	0	...	1	7	0	...
Weakness	0	...	1	7	0	...
Pain in arm	0	...	1	7	0	...

[a]Reprinted with permission from Fontaine et al.[30] [b]$p < .05$ (all comparisons with Fisher exact probability test, 1-tailed). [c]$p < .10$.
Abbreviation: GAD = generalized anxiety disorder.

either bromazepam or diazepam was discontinued after 4 weeks of treatment. Patients in both benzodiazepine groups experienced significantly greater worsening of anxiety ($p < .05$) than patients in the placebo group, and there was a nonsignificant ($p > .10$) trend toward a greater increase in anxiety after withdrawal of bromazepam than diazepam. The differences in potency and elimination half-life between bromazepam and diazepam may be responsible for rebound anxiety (see Table 1).

Gradual tapering rather than abrupt discontinuation can help to control withdrawal symptoms. The rate of reduction for the first 50% of a dose can be more rapid than the last 50%. By reducing the dose by 10% at 5- to 7-day intervals, a plateau period develops that can help to distinguish the development of recurrent, rebound, or withdrawal symptoms. Unfortunately, some patients discontinue without consulting their physician.

CNS withdrawal symptoms or new symptoms are generally minor in nature (e.g., insomnia, gastric problems, and tremors) and often develop when short to intermediate half-life benzodiazepines are discontinued (Table 3).[30] These symptoms are typically transient and last less than a week. New symptoms that are major in nature are very rare but may include seizures and psychosis and, in cases of barbiturate or narcotic abuse, death. With gradual taper, however, withdrawal seizures are rare and generally occur in patients taking a high dose for longer than 4 months. Patients with a history of seizure are more likely to be at risk for seizure than those who do not have a history of seizure. Concomitant use of drugs that may lower the seizure threshold also presents a risk. Most seizures occur at the end of taper. The risk of withdrawal symptoms and especially seizure is greater with benzodiazepines with short and intermediate half-lives. Short and intermediate half-life compounds carry greater risks for rebound, withdrawal reactions, and dependence than long-acting agents.[31,32] To reduce the risk of rebound anxiety, clinicians should consider prescribing benzodiazepines with a long half-life, such as diazepam, clorazepate, and clonazepam, and withdraw them gradually, over a few weeks. Clonazepam[12,24,33] and diazepam[27] have longer half-lives and fewer rebound and withdrawal symptoms than alprazolam.

AMNESTIC EFFECTS

The effects of benzodiazepines on memory have been well documented,[34] and differences in absorption rates, potency, dose, and route of administration all contribute to each drug's potential to impair memory.[35] Following drug administration, tests of immediate and delayed (20 to 90 minutes) recall of word lists showed that impairment was limited to delayed recall and that immediate recall was unaffected. The effects on recall are usually short lasting and reversible. The 2 benzodiazepines most frequently associated with amnestic effects are triazolam[36–38] and lorazepam.[39,40] Transient global amnesia or so-called traveler's amnesia has also been reported by patients taking triazolam.[41] Other benzodiazepines appear to have a similar effect on delayed recall, but severity of this effect varies from drug to drug. During chronic benzodiazepine administration, tolerance to memory effects appears to develop[42,43] and the impairment is limited to a narrow window within 90 minutes after each dose.[44]

The relative solubility of benzodiazepines contributes to memory impairment. The greater the lipid solubility, the greater the likelihood of memory damage. Whether administered intramuscularly (IM) or in its newest form as a disintegrating wafer, clonazepam has low lipid solubility and is least likely to cause memory impairment.

ANXIETY AND PANIC

Alprazolam was one of the first benzodiazepines to be studied for its efficacy in treating patients with generalized anxiety and panic disorders with the new DSM-III classification. In the first 8-week, double-blind, placebo-controlled study[12] of 30 outpatients with GAD and 20 outpatients with panic disorder (Research Diagnostic Criteria), we found alprazolam at dosages between 0.25 and 3.00 mg/day to be significantly more effective ($p < .05$) than placebo in treating either disorder. Sixteen patients with GAD and 14 patients with panic disorder received the active drug. Alprazolam treatment was associated with a quick response in both groups. Mean total scores on the HAM-A for patients with either disorder showed significant improvement in anxiety by the second week compared with placebo (GAD patients [$p = .08$]; panic disorder patients [$p = .001$]). No significant differences in response to alprazolam between the 2 diagnostic groups were found. Behavior therapy, which was conducted during the last 4 weeks in 18 patients, had little effect on outcome.

Clonazepam is a partial benzodiazepine agonist and a serotonin agonist, which may account for its efficacy at low concentrations. Like alprazolam, clonazepam has been effective in the treatment of panic in controlled studies.[13] In a 4-week, placebo-controlled study[45] of clonazepam, 11 patients with a diagnosis of DSM-III panic disorder and 18 patients with a diagnosis of agoraphobia with panic attacks were randomly assigned to clonazepam or placebo. In addition to being superior to placebo with respect to treating the symptoms of anxiety and depression ($p < .001$), at a mean ± SD dose of 2.2 ± 0.7 mg/day at week 4, clonazepam was associated with decreased frequency, intensity, and duration of panic attacks. The clonazepam concentration in plasma was significantly correlated ($p < .05$) with a decrease in the global measure of the severity of panic disorder, but no correlation existed between drug concentration in plasma and a decline in generalized anxiety. Furthermore, an antipanic effect was noted in the clonazepam group during the first week of treatment, and 2 of 12 patients in the clonazepam group were panic free during the final 2 weeks of treatment. These results are in agreement with the Boston group results.[46]

TREATMENT CONSIDERATIONS

Before initiating treatment with a benzodiazepine, each patient must be thoroughly screened for a history of drug or alcohol dependence before the onset of the anxiety disorder, and a family history of drug or alcohol dependence. Benzodiazepines should be used with caution in patients predisposed to drug or alcohol dependence. If drug tolerance develops during treatment with high-potency benzodiazepines (maximum dose, 2 mg/day), a selective serotonin reuptake inhibitor (SSRI) or an anticonvulsant could be added in small doses (e.g., gabapentin at 100–600 mg/day).

Other factors to consider in prescribing high-potency benzodiazepines include the relative lipid solubility, binding affinity, and half-life.[32] As mentioned, lipid solubility is associated with memory impairment. Diazepam,[35] triazolam,[36,47] alprazolam,[12] and lorazepam[35,48,49] have high lipid solubility (see Table 1)[18] and have been associated with cognitive impairment and anterograde amnestic effects. In vitro comparisons of compounds that have shown the greatest tendency toward memory loss tend to have the greatest affinity for the benzodiazepine receptor.[19] Benzodiazepine drugs with lower affinity for the benzodiazepine receptor tend to have less amnestic potential. Short and intermediate half-life compounds carry greater risks of memory loss than benzodiazepines with longer half-lives and, administered at high doses, are more likely to cause severe memory loss. Elimination half-life of benzodiazepines is shown in Table 1.[16] Relative lipid solubility and alpha distribution half-life will determine the duration of action after a single dose and after multiple doses (other parameters being equal).

Our studies[12,13] have shown that abrupt discontinuation of benzodiazepines can cause rebound anxiety in addition to new physical symptoms in patients with GAD. High-potency benzodiazepines were associated with a greater anxiolytic effect than the classic benzodiazepines. Alprazolam and clonazepam were effective for treating panic disorder, and clonazepam was effective as antimanic adjunctive treatment as well. Fatalities from benzodiazepine overdose alone are very rare. Benzodiazepines combined with a CNS depressant (e.g., alcohol, TCAs, barbiturates, or narcotics) place the patient at greater risk. In drug toxicity, clonazepam has been found to be one of the safest benzodiazepines.

Generalized Anxiety Disorder

Some factors to consider when selecting a benzodiazepine to treat anxiety include the rate of onset, distribution, and elimination (determines half-life at steady state) and the risk of withdrawal and rebound effects. As an early step toward preventing discontinuation syndrome, clinicians can prescribe benzodiazepines with long half-lives or the anticonvulsant gabapentin. At the end of treatment, clinicians can gradually withdraw the benzodiazepine over a period of a few weeks. A slow taper, rather than abrupt discontinuation, dramatically decreases the incidence of untoward symptoms.

For mild-to-moderate nonrecurrent GAD, a medium-potency benzodiazepine with a long half-life plus a nonbenzodiazepine anxiolytic or a hypnotic may be effective and lead to the fewest undesirable effects. Patients with severe and chronic GAD, however, may respond better to a high-potency benzodiazepine plus gabapentin or an SSRI.

Panic Attacks and Panic Disorder

Panic attacks are not specific to patients with panic disorder. They can occur in OCD and social phobia as well.

Since panic attacks can mask depression, they should be treated immediately. Panic attacks may be secondary to an underlying medical condition, a medication side effect, or illicit drug use. Numerous randomized controlled trials[10–12,24–26] show that high-potency benzodiazepines are efficacious in the acute treatment of panic disorder (including panic attack), but clinical issues should be considered. Clonazepam, for example, with its long half-life and few rebound and withdrawal symptoms,[12] may be a better choice than alprazolam, which has a short half-life and more rebound and withdrawal symptoms.[24] If the response to either alprazolam or clonazepam is incomplete at a maximum dose of 2 mg/day, adjunctive therapy with an SSRI at a low dose that may be gradually increased is recommended. An anticonvulsant such as gabapentin may also be added. Further, benzodiazepines have been effective in the long-term management of panic disorder at low doses (should the attacks develop into a full disorder), are as effective as SSRIs in treating panic disorder, and have been effective in combination with SSRIs. Finally, some patients with panic disorder benefit from cognitive-behavioral therapy combined with pharmacotherapy.

Obsessive-Compulsive Disorder

Clomipramine is seldom used to treat OCD because of its tricyclic toxicity, side effects, lethality in overdose, and withdrawal rebound effects. However, clomipramine may have slightly greater efficacy than other non-SSRI antidepressants.[50] Its highly potent (but not specific) inhibition of serotonin reuptake (as compared with SSRIs) may be the source of its effect. SSRIs may be even more effective in treating patients with OCD when used in conjunction with clonazepam, especially since higher doses of SSRIs are needed and several weeks and even months of treatment are necessary.[51]

Agitation and Mania

The management of agitated, potentially dangerous patients is a common problem. Prior to the advent of antipsychotic drugs, treatment of these patients relied on barbiturates. Then chlorpromazine was introduced and later combined with phenobarbital sodium, establishing the principle of combining an antipsychotic and a sedative hypnotic.[52] Haloperidol and other high-potency benzodiazepines later replaced chlorpromazine, but not until a reliably absorbed IM form of lorazepam became available was it possible to replace barbiturates with a benzodiazepine.[52] Lorazepam and clonazepam have been the most widely studied benzodiazepines in patients with acute agitation and mania. Several clinical trials[52–54] have consistently shown that the combination of lorazepam and haloperidol is more effective than either agent alone in achieving rapid control of aggressive, psychotic behavior. Some studies[55,56] of lorazepam monotherapy versus haloperidol monotherapy in psychotic patients have shown lorazepam to be at least as efficacious as haloperidol. Lorazepam plus lithium has also been shown to be effective in treating patients with acute mania.[15]

Clonazepam is highly sedative and well tolerated at high doses in treating patients with acute mania.[10] Clonazepam was more effective than lithium in reducing manic symptoms but more importantly, as needed doses of haloperidol were fewer and the number of days it was needed was lower during clonazepam treatment than during lithium treatment. By reducing the need for anticonvulsants and antipsychotics in the treatment of acute mania, clonazepam reduces the risk of side effects in these patients. Compared with IM haloperidol,[57] IM clonazepam monotherapy is effective and safe but slower acting. In countries such as the United States where IM clonazepam is not available, clonazepam wafers are a good alternative since they are easy to administer and do not carry some of the problems associated with lorazepam (dependence associated with rebound and amnesia).

Adjunctive high-potency benzodiazepines have become the standard treatment for patients with agitation or acute psychosis, or who become dangerous to themselves and others. A large multicenter trial[53] confirmed several other controlled studies and established the potentiating effect of benzodiazepines when given with haloperidol at the emergency department for acute agitation. A recent literature review[58] further supports the use of parenteral benzodiazepines to achieve rapid tranquilization; however, atypical antipsychotics such as risperidone, ziprasidone, and olanzapine with or without benzodiazepines should be considered first in the treatment of acute agitation.[59] The combination of a classic antipsychotic and a benzodiazepine is another reasonable alternative. Whenever possible, an oral treatment, such as disintegrating wafers, should be offered first to help build an alliance with the patient and suggest an internal rather than external locus of control.[59]

CONCLUSION

High-potency benzodiazepines have become the preferred method of treatment for anxiety and panic disorders with or without agoraphobia owing to their anxiolytic effect and rapid onset of action. Clinical issues, such as dependence, rebound anxiety, discontinuation syndrome, and memory impairment, must be taken into consideration when choosing one of them. Rebound anxiety, withdrawal reactions, and dependence appear to be greater among patients taking benzodiazepines with short-to-intermediate elimination half-lives than those taking agents with long half-lives. Memory impairment has been associated with several high-potency benzodiazepines and appears to be related to lipid solubility associated with their high affinity for benzodiazepine receptors. As adjunctive treatment, high-potency benzodiazepines have been given with SSRIs in panic disorder and OCD, and with antipsychotics in acute agitation and acute mania.

Drug names: alprazolam (Xanax), chlordiazepoxide (Limbitrol, Librium, and others), chlorpromazine (Thorazine, Sonazine, and others), clomipramine (Anafranil), clonazepam (Klonopin), clorazepate (Gen-Xene, Tranxene, and others), diazepam (Diastat, Valium, and others), estazolam (Prosom), flurazepam (Dalmane), gabapentin (Neurontin), haloperidol (Haldol), lorazepam (Ativan), olanzapine (Zyprexa), oxazepam (Serax), quazepam (Doral), risperidone (Risperdal), temazepam (Restoril), triazolam (Halcion), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, clonazepam is not approved by the U.S. Food and Drug Administration for the treatment of agitation, and gabapentin is not approved for the treatment of anxiety and panic disorders.

REFERENCES

1. Chouinard G, Annable L. Clozapine in the treatment of newly admitted schizophrenic patients: a pilot study. J Clin Pharmacol 1976;133:820–823
2. Chouinard G et al. Tryptophan-nicotinamide in depression [letter]. Lancet 1977;1:249
3. Chouinard G et al. Tryptophan dosage critical for its antidepressant effect [letter]. Br Med J 1978;1:1422
4. Chouinard G et al. Tryptophan-benserazide in the treatment of schizophrenia. Commun Psychopharmacol 1978;2:21–31
5. Chouinard G et al. Tryptophan-nicotinamide in the treatment of newly admitted depressed patients. Commun Psychopharmacol 1978;2:311–318
6. Chouinard G et al. Tryptophan-nicotinamide, imipramine and their combination in depression. Acta Psychiatr Scand 1979;59:395–418
7. Chouinard G et al. Potentiation of lithium by tryptophan in a patient with bipolar illness. Am J Psychiatry 1979;136:719–720
8. Chouinard G et al. Tryptophan in the treatment of depression and mania. In: van Pragg HM, Mendlewicz J, eds. Advances in Biological Psychiatry, vol 10. Basel, Switzerland: Karger; 1983:47–66
9. Chouinard G et al. A controlled clinical trial of L-tryptophan in acute mania. Biol Psychiatry 1985;20:546–557
10. Chouinard G et al. Antimanic effect of clonazepam. Biol Psychiatry 1983;18:451–466
11. Chouinard G et al. Alprazolam in the treatment of generalized anxiety and panic disorders: a double-blind placebo-controlled study. Psychopharmacol Bull 1983;19:115–116
12. Chouinard G et al. Alprazolam in the treatment of generalized anxiety and panic disorders: a double-blind placebo-controlled study. Psychopharmacology (Berl) 1982;77:229–233
13. Chouinard G et al. New concepts in benzodiazepine therapy: rebound anxiety and new indications for the more potent benzodiazepines. Prog Neuropsychopharmacol Biol Psychiatry 1983;7:669–673
14. Lenox RH et al. Acute treatment of manic agitation with lorazepam. Psychosomatics 1986;27(suppl 1):28–32
15. Modell JG et al. Inpatient clinical trial of lorazepam for the management of manic agitation. J Clin Psychopharmacol 1985;5:109–113
16. Nelson J, Chouinard G. Guidelines for the clinical use of benzodiazepines: pharmacokinetics, dependency, rebound and withdrawal. Can J Clin Pharmacol 1999;6:69–83
17. AHFS Drug Information. Available at: www.ashp.org/ahfs. Accessed Jan 26, 2004
18. Ochs HR et al. Bromazepam pharmacokinetics: influence of age, gender, oral contraceptives, cimetidine, and propranolol. Clin Pharmacol Ther 1987;41:562–570
19. Greenblatt DJ et al. Clonazepam pharmacokinetics, brain uptake, and receptor interactions. J Clin Psychiatry 1987;48(suppl 10):4–9
20. Chouinard G et al. Gabapentin: long-term antianxiety and hypnotic effects in psychiatric patients with comorbid anxiety-related disorders [letter]. Can J Psychiatry 1998;43:305
21. Davidson JR et al. Treatment of social phobia with clonazepam and placebo. J Clin Psychopharmacol 1993;13:423–428
22. Pande AC et al. Placebo-controlled study of gabapentin treatment of panic disorder. J Clin Psychopharmacol 2000;20:467–471
23. Rosenbaum JF. The development of clonazepam as a psychotropic: the Massachusetts General Hospital experience. J Clin Psychiatry 2004;65 (suppl 5):3–6
24. Fontaine R, Chouinard G. Antipanic effect of clonazepam [letter]. Am J Psychiatry 1984;141:149
25. Beaudry P et al. An open clinical trial of clonazepam in the treatment of patients with recurrent panic attacks. Prog Neuropsychopharmacol Biol Psychiatry 1985;9:589–592
26. Beaudry P et al. Clonazepam in the treatment of patients with recurrent panic attacks. J Clin Psychiatry 1986;47:83–85
27. Chouinard G. Rebound anxiety: incidence and relationship to subjective cognitive impairment. J Clin Psychiatry Monograph 1986;4:12–16
28. Chouinard G. Additional comments on benzodiazepine withdrawal. Can Med Assoc J 1988;139:119–120
29. Wilens T. ADHD and substance abuse. In: Spencer T, ed. Adult ADHD. Philadelphia, Pa: Psychiatric Clinics of North America. In press
30. Fontaine R et al. Rebound anxiety in anxious patients after abrupt withdrawal of benzodiazepine treatment. Am J Psychiatry 1984;141:848–852
31. Teboul E, Chouinard G. A guide to benzodiazepine selection, pt 1: pharmacological aspects. Can J Psychiatry 1990;35:700–710
32. Teboul E, Chouinard G. A guide to benzodiazepine selection, pt 2: clinical aspects. Can J Psychiatry 1991;36:62–73
33. Wolf B, Griffiths RR. Physical dependence on benzodiazepines: differences within the class. Drug Alcohol Depend 1991;29:153–156
34. Woods JH et al. Benzodiazepines: use, abuse and consequences, 4: adverse behavioral consequences of benzodiazepine use. Pharmacol Rev 1992;44:207–237
35. Healey M et al. Effects of clorazepate, diazepam, lorazepam, and placebo on human memory. J Clin Psychiatry 1983;44:436–439
36. Bixler EO et al. Next-day memory impairment with triazolam use. Lancet 1991;337:827–831
37. Weingartner HJ et al. Specificity of memory impairments with triazolam use [letter]. Lancet 1991;338:883–884
38. Kirk T et al. Dose-response evaluation of the amnestic effects of triazolam and pentobarbital in normal subjects. J Clin Psychopharmacol 1990;10:160–167
39. Scharf MB et al. Differential amnestic properties of short- and long-acting benzodiazepines. J Clin Psychiatry 1984;45:51–53
40. Brown J, Lewis V. A comparison between transient amnesias induced by two drugs (diazepam or lorazepam) and amnesia of organic origin. Neuropsychologia 1982;20:55–70
41. Morris HH III, Estes ML. Traveler's amnesia: transient global amnesia secondary to triazolam. JAMA 1987;258:945–946
42. Peedicayil J et al. The effect of diazepam on memory in a group of patients with anxiety neurosis. Curr Ther Res Clin Exp 1988;44:385–390
43. Golombok S et al. Cognitive impairment in long-term benzodiazepine users. Psychol Med 1988;18:365–374
44. Lucki I, Rickels K. The effect of anxiolytic drugs on memory in anxious subjects. Psychopharmacol Bull 1988;6:128–139
45. Beauclair L et al. Clonazepam in the treatment of panic disorder: a double-blind, placebo-controlled trial investigating the correlation between clonazepam concentrations in plasma and clinical response. J Clin Psychopharmacol 1994;14:111–118
46. Pollack MH et al. Longitudinal course of panic disorder: findings from the Massachusetts General Hospital Naturalistic Study. J Clin Psychiatry 1990;51(12, suppl A):12–16
47. Spinweber CL, Johnson LC. Effects of triazolam (0.5 mg) on sleep, performance, memory, and arousal threshold. Psychopharmacology (Berl) 1982;76:5–12
48. Mac DS et al. Anterograde amnesia with oral lorazepam. J Clin Psychiatry 1985;46:137–138
49. Scharf MB et al. Anterograde amnesia with oral lorazepam. J Clin Psychiatry 1983;44:362–364
50. Greist J et al. Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. Arch Gen Psychiatry 1995;52:289–295
51. Pigott TA et al. A controlled trial of clonazepam augmentation in OCD patients treated with clomipramine or fluoxetine. In: New Research Program and Abstracts of the 145th Annual Meeting of the American Psychiatric Association; May 4, 1992; Washington, DC. Abstract NR144:82
52. Garza-Trevino ES et al. Efficacy of combinations of intramuscular antipsychotics and sedative-hypnotics for control of psychotic agitation. Am J Psychiatry 1989;146:1598–1601
53. Battaglia J et al. Haloperidol, lorazepam, or both for psychotic agitation? a multicenter, prospective, double-blind, emergency department study. Am J Emerg Med 1997;15:335–340
54. Bietniek SA et al. A double-blind study of lorazepam versus the combination of haloperidol and lorazepam in managing agitation. Pharmacotherapy 1998;18:57–62
55. Salzman C et al. Parenteral lorazepam versus parenteral haloperidol for the control of psychotic disruptive behavior. J Clin Psychiatry 1991;52:177–180
56. Foster S et al. Efficacy of lorazepam and haloperidol for rapid tranquilization in a psychiatric emergency room setting. Int Clin Psychopharmacol 1997;12:175–179
57. Chouinard G et al. A double-blind randomized clinical trial of rapid tranquilization with I.M. clonazepam and I.M. haloperidol in agitated psychotic patients with manic symptoms. Can J Psychiatry 1993;38 (suppl 4):S114–S121
58. McAllister-Williams RH, Ferrier IN. Rapid tranquillisation: time for a reappraisal of options for parenteral therapy. Br J Psychiatry 2002;180:485–489
59. Yildiz A et al. Pharmacological management of agitation in emergency settings. Emerg Med J 2003;20:339–346