



GUIDELINES FOR THE USE OF BENZODIAZEPINES IN OFFICE PRACTICE IN THE STATE OF MAINE

Introduction: This is an evidence-based guideline for the use of benzodiazepines and related drugs in clinical office practice. Attached is a bibliography including earlier guidelines on which this guideline is partially based and websites, reviews, and clinical studies that provide supporting evidence. This guideline applies to benzodiazepines used primarily as anxiolytics and sedative/hypnotics, and to the related Z drugs, such as zolpidem, which, while structurally different from the benzodiazepines, produce similar pharmacologic effects and have similar dependence and abuse potential.

The patient and his healthcare providers should agree on one provider to be the designated BZD prescriber for that patient. This designated prescriber will also be responsible for prescribing other medications with abuse potential, specifically central nervous system stimulants and narcotics, keeping in mind that the use of BZDs with long-term narcotics and stimulants is not recommended. .

Patients receiving a new prescription for a BZD for anxiety should be advised on nondrug therapies. Counseling referral will be strongly recommended.

Risks and side effects of BZDs should be reviewed, including the risk of dependence. In the patient over 65, these include the risk of falls, cognitive impairment, and interactions with other medications and medical conditions. Therefore BZDs should be used with caution in this age group. Because of delayed metabolism and increased risk of side effects, BZDs should be initiated at one-half of the usual adult starting dose in the elderly patient.

Prescription BZDs are often diverted. Care should be taken when prescribing to reduce the risk of diversion.

When initiating a course of BZD treatment, the clinician should keep in mind that some patients will have difficulty discontinuing the medication at the end of the acute treatment period. At the initiation of treatment, the patient should be advised explicitly regarding the duration of treatment. Exit strategies, such as a short taper or initiation of alternative treatments, may be discussed. If the patient's past medication use patterns or history of substance abuse suggest that BZD discontinuation may be problematic, then alternatives to BZDs should be utilized.

1. Contra-indications to BZDs (particularly for long-term use)

- a) Pregnancy and the patient at risk for pregnancy. BZDs are category D. If a hypnotic is necessary, Zolpidem (Ambien), which is category B, is preferred. Patients who conceive while on BZDs should be tapered off completely or to the lowest possible dose.
- b) Active substance abuse, including alcohol.
- c) Medical and mental health problems that may be aggravated by BZDs. These include fibromyalgia, chronic fatigue syndrome, other somatization disorders, depression (except for short-term use to treat associated anxiety), bipolar disorder (except for urgent sedation in acute mania), ADHD, kleptomania, and other impulse control disorders. They may worsen hypoxia and hypoventilation in asthma, sleep apnea, COPD, CHF, and other cardiopulmonary disorders.
- d) Patients being treated with opioids for chronic pain or replacement therapy for narcotic addiction.
- e) Grief reactions. BZDs are often used for short term treatment of insomnia in acute grief but should otherwise be avoided in treating grief reactions, as they may suppress and prolong the grieving process.

2. Indications for short-term treatment with benzodiazepines

- a) The principal indication for BZDs is for short-term treatment (2 to 6 weeks) of anxiety disorders. These conditions include generalized anxiety disorder, phobias, PTSD, panic disorder, and severe anxiety associated with depression, while waiting for the full effect of the antidepressant. While BZDs have been studied and utilized to treat these conditions they are not first-line therapy for any of them. However, it is acceptable to use BZDs as adjuncts during initial treatment while waiting for definitive therapy with long-term medications and/or counseling to take hold. Continuing BZDs beyond 4 to 6 weeks will result in loss of effectiveness, the development of tolerance, dependence and potential for withdrawal syndromes, persistent adverse side effects, and interference with the effectiveness of definitive medication and counseling. BZDs taken for more than 2 weeks continuously should be tapered rather than discontinued abruptly.

b) Insomnia

There is evidence for the effectiveness of BZDs and other hypnotics in the relief of short-term (1 to 2 weeks), but not long-term, insomnia. The treatment period should not exceed 2 weeks. The only significant clinical difference between older BZD hypnotics and the newer ones—zolpidem (Ambien), zaleplon (Sonata), and eszopiclone (Lunesta) -- is the shorter half-life of zolpidem and zaleplon (2 hours). All three have similar risks of dependence

and tolerance. A search for an etiology of the insomnia should be undertaken. Sleep hygiene measures should be discussed.

c) Muscle relaxant

BZDs or other muscle relaxants are indicated for the short-term relief (1 to 2 weeks) of muscular discomfort associated with acute injuries or flare-ups of chronic musculoskeletal pain. BZDs may be combined with analgesics and non-drug therapies but not with other sedatives, hypnotics, or other muscle relaxants.

d) Other Indications:

Urgent treatment of acute psychosis with agitation
As part of a protocol for treating alcohol withdrawal
Adjunctive treatment of withdrawal from other addictions (less accepted)
Single-dose treatment of phobias, such as flying phobia
Seizures and a limited number of other neurological disorders
Sedation for office procedures

3. Indications for long-term treatment with benzodiazepines.

BZDs may be used for longer than 6 weeks in the terminally ill, in the severely handicapped patient, in certain neurological disorders (stiff-person syndrome), and as an alternative to antipsychotics in the severely demented patient.

4. Approach to the patient already on long-term benzodiazepines.

There is no evidence supporting the long-term use of BZDs for any mental health indication. At the time of BZD prescription renewal or medication review, the physician should discuss the risks of long-term BZDs and the benefits of discontinuation (on cognition, mood, sleep, and energy level) and advise the patient to reduce or discontinue the BZD. For some patients this will be difficult or impossible, but the effort should be made. For many a reduction in dose, rather than discontinuation, will be the goal.

Those who can be persuaded to do so should attempt a taper of their current BZD or hypnotic. The taper should be slow—starting with ½ of a tablet every 2 weeks (or 10 to 12% of the daily dose if the BZD is taken once daily). Exceptions to this are zolpidem and zaleplon, which may be tapered more quickly or even stopped abruptly since their half-life is short. Eszopiclone has a half-life in the range of short-acting BZDs (6 hrs) so will need to be tapered. The patient should direct the taper as much

as is feasible. Some may accomplish this with limited physician input. Others will benefit from a more structured framework of periodic physician visits, with the physician closely supervising the tapering schedule. The rate of tapering should be individualized. The process may take 3 to 12 months to complete.

If this is not successful or if it is preferred, the patient can be switched to an equivalent dose of a long-acting BZD (diazepam or chlordiazepoxide) or phenobarbital and then tapered off. If a switch is made, it should be stepwise—one dose every one to two weeks if the patient is on multiple daily doses. The tapering process may begin during the conversion. See the table below for dose equivalents that may be used for this conversion.

Because they share GABAergic receptor activity with BZDs, several anticonvulsants (carbamazepine, valproate, gabapentin) can be used to facilitate rapid BZD withdrawal. While on a maintenance dose of the anticonvulsant, a rapid taper of the BZD can be undertaken over three days to two weeks. The anticonvulsant will be continued for 2 to 3 months and then tapered.

Counseling should be available to assist with the withdrawal process. The counselor may be utilized to treat the underlying condition for which the BZD was prescribed, to address personal crises which may derail the tapering schedule, and to deal with rebound anxiety.

For a more detailed discussion of how to withdraw patients from BZDs, visit the website www.benzo.org.uk.

5. Special Considerations

- a) Care should be taken not to taper alprazolam too rapidly, nor to switch from it to another BZD too abruptly, as withdrawal seizures are more prone to occur with it than with other BZDs.
- b) Patients who have previous addiction problems, are on high doses of BZDs, or who are taking opiates or amphetamines concurrently will be more difficult to withdraw and may benefit from referral to an addiction specialist.
- c) As patients age they will become more sensitive to the same dose of a BZD and have higher risks of adverse effects, so aging patients unable to discontinue long-term BZDs should at least have their dose reduced.
- d) There is some risk in driving and operating dangerous machinery even with stable doses of BZDs. Those with increased risk, including a recent dose increase, concomitant use of other sedative medications, high doses, or observed sedating effects should be cautioned not to drive. Occasionally it will be necessary to notify the state Division of Motor Vehicles.

EQUIVALENCE TABLE TO BE USED FOR SUBSTITUTION DURING WITHDRAWAL

Alprazolam (Xanax)	0.5 mg
Chlordiazepoxide (Librium)	25 mg
Clonazepam (Klonopin)	0.5 mg
Diazepam (Valium)	10 mg
Lorazepam (Ativan)	1 mg
Temazepam (Restoril)	20 mg
Zolpidem (Ambien)	20 mg
Zaleplon (Sonata)	20 mg
Eszopiclone (Lunesta)	3 mg

BIBLIOGRAPHY FOR MAINE BENZODIAZEPINE GUIDELINES

PUBLISHED GUIDELINES

www.state.ky.us/agencies/kbml/policy/benzo.pdf

A succinct and practical guideline from the Kentucky Medical Licensing Board

www.racgp.org.au/guidelines/benzodiazepines/

Guidelines from Australia

www.le.ac.uk/cgrdu/benzo-ct17.pdf

This site contains a set of audit criteria for appropriate benzodiazepine use

www.benzo.org.uk

Large site that is consumer-oriented, but of interest to clinicians also. Useful information on BZD withdrawal, links to other sites.

See the page “Benzodiazepines around the world”.

www.nice.org.uk

This site contains a guideline for anxiety disorders that is long and comprehensive. It comes with an extensive, up-to-date bibliography.

www.dohc.ie/publications

Department of Health and Children (Ireland) August 2002
Report of the Benzodiazepine Committee

www.uptodate.com

This widely used reference, available by paid subscription, discusses recommended evaluation and treatment of common mental health diagnoses

Ashton, Heather
Guidelines for the rational use of benzodiazepines
Drugs 1994; 48(1)

Australian and New Zealand clinical practice guidelines for the treatment of panic disorder and agoraphobia
Australian and New Zealand Journal of Psychiatry 2003; 37:641-656

Guidelines for the prevention and treatment of benzodiazepine dependence: Summary of a report from the Mental Health Foundation (UK)
Addiction (1993) 88, 1707-1708

Muller JE et al
Social anxiety disorder: current treatment recommendations
CNS Drugs 2005; 19(5): 377-91

Van Ameringen M et al
World Council of Anxiety recommendations for the long-term treatment of social phobia
CNS Spectrum 2003; Aug 8 (8 SUPPL 1) 40-52

Pollack MH et al
World Council of Anxiety recommendations for the long-term treatment of panic disorder
CNS Spectrum 2003; Aug 8 (8 SUPPL 1) 17-30

REVIEWS AND META-ANALYSES

Holbrook Anne, Crowther Renee, Lotter Ann, Cheng Chiachen, King Derek
Treatment of Insomnia
CJAM 2000; 16, 162920: 211-225

Van Lalkom AJ, Bakker A, Spinhover P, et al
A meta-analysis of the treatment of panic disorder with or without agoraphobia: a comparison of psychopharmacological, cognitive-behavioral, and combination treatments
Journal of Nervous and Mental Disease 1997; 185: 8.510-516

Bakker A, van Balkom AJ, Spinhoven P et al
Follow-up on the treatment of panic disorder with or without agoraphobia: a quantitative review
Journal of Nervous and Mental Disease 1998;186:7.414-419

Otto MW et al
Empirically supported treatments for panic disorder: costs, benefits and stepped care
Journal of Consulting and Clinical Psychology 2000; 68: 556-563

Gould RA, Otto MW, Pollack MH, et al
Cognitive behavioral and pharmacological treatment of generalized anxiety disorder: a preliminary meta-analysis
Behavior Therapy 1997; 28: 285-305

Roerig JL
Diagnosis and management of generalized anxiety disorder
Journal of the American Pharmaceutical Association 1999; 39: 6.811-821

Davidson JRT, Ballenger JC, Lecrubier Y, et al
Pharmacotherapy of generalized anxiety disorder
Journal of Clinical Psychiatry 2001; 62: SUPPL. 11: 46-52

Barker MJ
Cognitive effects of long-term benzodiazepine use: a meta-analysis
CNS Drugs 2004; 18(1): 37-48

Furukawa TA et al
Antidepressants and benzodiazepines for major depression
Cochrane Database Syst Rev 2001; 2: CD 001026

Cummings RG, LeCouteur DG
Benzodiazepines and the risk of hip fracture in older people: a review of the evidence
CNS Drugs 2003; 17(11); 825-837

Lydiard RB
An overview of generalized anxiety disorder disease state: appropriate therapy
Clinical Ther 2000; 22 SUPPL A: A3-19

Wagstaff AJ et al
Paroxetine- an update of its use in psychiatric disorders in adults
Drugs 2002; 62: 4.655-703

Pollack MH

Optimizing Pharmacotherapy of generalized anxiety disorder to achieve remission
Journal of Clinical Psychiatry 2001; 62 SUPPL 19: 20-25

Butler AC, Chapman JE, Forman EM, Beck A
The empirical status of cognitive-behavioral therapy: a review of meta-analyses
Clin Psychol Rev 2005 Sept 29 (in press)

RELEVANT STUDIES

Below are a few recent studies involving outcomes of long-term benzodiazepine therapy, issues around discontinuation, combining benzodiazepines with psychological therapies, and other studies that are unique and relevant. A review of Medline reveals numerous studies addressing short-term use of benzodiazepines in various mental health disorders and as muscle relaxants, cognitive effects of benzodiazepines, other problems with benzodiazepines in geriatric patients, and effects of benzodiazepines on driving and injury risk, which will not be listed here.

Power KG
A controlled comparison of cognitive-behavior therapy, diazepam, and placebo. Alone and in combination, for the treatment of generalized anxiety disorder
Journal of Anxiety Disorders 1990; 4; 4.267-292 Vashaar RC et al

Alprazolam revisited
Medical Letter of Drugs and Therapeutics 2005 Jan 17; 47(1208): 5-7

Zolpidem is not superior to temazepam with respect to rebound insomnia: a controlled study
European Neuropsychopharmacology 2004 Aug; 14(4): 301-306

The following studies examine the negative influence of benzodiazepines on psychological therapies, particularly when used on an as-needed basis.

Van Balkom AJ, de Beurs E, Loele P, et al
Long-term benzodiazepine use is associated with smaller treatment gain in panic disorder with agoraphobia
Journal of Nervous and Mental Disease 1997; 185: 8.510-516

Westra HA, Stewart SH, Conrad BE
Naturalistic manner of benzodiazepine use and cognitive behavioral therapy outcome in panic disorder with agoraphobia
Journal of Anxiety Disorders 2002; 16: 3.233-246

In this study of diazepam vs. placebo for GAD demonstrating only short-term benefit from

diazepam, the diazepam group doesn't suddenly worsen after 3 weeks, but rather the placebo group catches up.

Pourmotabbed T, McLeod DR, et al

Treatment, discontinuation, and psychomotor effects of diazepam in women with generalized anxiety disorder

Journal of Clinical Psychopharmacology 1996; 16: 202-297 Reference ID: 70

This study suggests that benzodiazepines increase the risk of relapse in the alcoholic.

Poulos CX, Zack M

Low-dose diazepam primes motivation for alcohol and alcohol-related semantic networks in problem drinkers

Behavioral Pharmacology 2004 Nov; 15(7): 503-512

The following studies address outcomes of benzodiazepine discontinuation:

Vorma H et al

Long-term outcome after benzodiazepine withdrawal treatment in subjects with complicated dependence

Drug and Alcohol Dependence 2003 June 5; 70(3): 309-315

Morin CM et al

Long-term outcome after discontinuation of benzodiazepines for insomnia

Behav Res Ther 2005 Jan; 43(1) 1-14

Oconnor KP et al

Psychological distress and adaptational problems associated with benzodiazepine withdrawal

Addict Behav 2004 May 29; (8) 583-593

Connor KM et al

Discontinuation of clonazepam in the treatment of social phobia

Journal of Clinical Psychopharmacology 1998 Oct 18(5); 373-378

These studies examine the long-term prognoses of anxiety disorders and the long-term outcomes of various treatments.

Adersch S, Hetta J

A 15-year follow-up study of patients with panic disorder

European Psychiatry 2003 Dec; 18(8): 401-408

Swoboda H, Amering M, et al

The long-term course of panic disorder—an 11-year follow-up

Journal of Anxiety Disorders 2003; 17(2): 223-232

Durham RC, Chambers JA, MacDonald RR et al
Does cognitive-behavioural therapy influence the long-term outcome of generalized anxiety disorder? An 8-14 year follow-up of two clinical trials
Psychological Medicine 2003; 33: 499-509