

# The Current Role of Long-Term Benzodiazepines for the Treatment of Generalized Anxiety

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**Current role**

Benzodiazepines are one of the most widely used medications for the treatment of generalized anxiety. Due to their quick onset of action, efficacy and tolerability, benzodiazepines are widely prescribed by clinicians and utilized by patients. Although benzodiazepines have been beneficial and effective for the short-term management of anxiety, they have not been shown to be effective in producing long-term improvement. Chronic use of benzodiazepines has demonstrated multiple side effects including cognitive impairment, decreased motor coordination, concentration, social phobia, and depression. The development of tolerance, dependence and withdrawal are some of most significant problems associated with the long-term use of benzodiazepines. Withdrawal associated with the use of benzodiazepines includes insomnia, agitation, anxiety, seizures and coma.

## INTRODUCTION

Generalized anxiety disorder (GAD) may be treated with different classes of medications such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antihistamines, barbiturates, and benzodiazepines. Prescribed for a multitude of medical conditions (anxiety, agitation, panic disorder, alcohol withdrawal, dystonia, insomnia, etc.) benzodiazepines have been approved for many indications.<sup>1</sup> While much is known about the safety and efficacy of benzodiazepines for the short-term treatment of GAD, there is limited data to guide decisions for the extended duration of benzodiazepine therapy for this medical condition.<sup>2</sup>

## GENERALIZED ANXIETY DISORDER

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM V), the diagnosis of GAD involves tension, worries, and fears about everyday events and problems on most days of the week for at least six months. The inclusion of the following criteria must also be met: anxiety or worry that interferes with daily life, anxiety that isn't related to another mental disorder (post traumatic stress disorder, substance abuse, etc.) and difficulty controlling worry. Additionally, at least three of the following must be present in adults or one of the following in children to contribute to the diagnosis of GAD: difficulty with concentration, problems falling or staying asleep, irritability, muscle tension, feeling of restlessness and unusual fatigue. Other generalized symptoms may also occur.<sup>3</sup>

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## FINDING A ROLE FOR LONG TERM BENZODIAZEPINES

There is controversy regarding the long-term use of benzodiazepines due to the adverse physical and psychological effects, tolerance, physical dependence and eventually withdrawal symptoms that can occur with cessation of treatment with this category of medication. Known for their rapid onset of action and clinical effectiveness over the short term, benzodiazepines can be used during the initiating phase of an SSRI or SNRI.<sup>4</sup> In the decision tree below, note the role of benzodiazepines in the management of anxiety.

**Table 1: Generalized Anxiety Disorder<sup>5</sup>**

<b>Target Symptoms:</b>	Subjective with anxiety/tension, excessive worry, and a variety of physiological complaints (GI, musculoskeletal, neurological)
<b>Medication Treatment:</b>	<p>Start with SSRIs in doses higher than for depression.</p> <ul style="list-style-type: none"> <li>• Escitalopram (Lexapro) 10-25 mg Once Daily</li> <li>• Sertraline (Zoloft) 50-150 mg Once Daily</li> <li>• SNRIs in usual doses</li> </ul> <p>Or</p> <p>VenlafaxineXR (EffexorXR) 75-225 mg Daily</p> <p>Or</p> <p>Buspirone (Buspar) 5-15 mg TID Alone or adjunct to above.</p> <p><i>Note: often 6-8 weeks before evident response.</i></p> <p>Or</p> <p>Benzodiazepines may be used alone or in combination for ongoing treatment or in management of periods of exacerbation</p> <p>Clonazepam (Klonopin) 1-2 mg up to TID</p>
<b>Psychotherapy:</b>	Referral to outside or co-located professional for cognitive behavioral psychotherapy may be effective as adjunct or in lieu of medication.

In the short term, benzodiazepines can be used with antidepressants in a combined effort since antidepressants take weeks to work. During the first several weeks of antidepressant therapy, benzodiazepines can help alleviate the nervousness with starting antidepressants. When the effect of an antidepressant begins to take effect, the benzodiazepine can be tapered off. In certain instances, benzodiazepines may be continued for the long term in patients who cannot tolerate tapering. Additionally, intermittent therapy may be needed in patients who have periodic symptoms initiated by identifiable anxiety provoking situations.

Long-term use of benzodiazepines is defined as use for two months or more at therapeutic dose. As most clinical trials on anxiolytic therapy are four weeks or less, few placebo-controlled trials exist to extrapolate the long-term effects of benzodiazepines in anxiety. Long term placebo-controlled trials are difficult from an ethical standpoint as they put a patient with psychiatric needs in the uncomfortable position of using a placebo or ineffective medication.<sup>6</sup> To ask if there is a role of long term benzodiazepines for anxiety begins with appreciating the spectrum of benzodiazepine half-lives and their pharmacokinetics.

## PHARMACOKINETICS

When looking at the potential of their clinical effectiveness, the pharmacokinetics of benzodiazepines should always play a role in defining an appropriate therapeutic regime. The lipid solubility of benzodiazepines determines the speed of entry into lipid tissue of the brain, followed by their redistribution into adipose tissue. Known to depress the central nervous system at the levels of the limbic system and the brain-stem reticular formation, as well as through their binding to the GABA-chloride receptor complex, benzodiazepines facilitate the action of GABA, an inhibitory neurotransmitter on CNS excitability. Benzodiazepines enhance the effect of GABA resulting in hypnotic, sedative, anxiolytic, anticonvulsant, amnestic and muscle relaxant properties.

The lipid solubility of benzodiazepines creates a high volume of distribution, resulting in the tissue drug concentration at a higher level than the blood drug concentration. Metabolized primarily through hepatic microsomal oxidation and demethylation, benzodiazepines are excreted by conjugation. Following conjugation, benzodiazepines become the more polar, water-soluble glucuronide derivatives. Patient age, smoking, liver disease, and concurrent use of other drugs may change the volume of distribution and the elimination half-life of benzodiazepines.

As we consider the differences in the short versus the long-term use of benzodiazepines for the treatment of GAD, we

note that generally the longer the half-life of the drug, the greater the likelihood the compound will have on daytime functioning. In shorter half-life drugs, withdrawal and anxiety between doses along with anterograde amnesia are more common. Short acting agents are generally used as hypnotics and for acute anxiety. Agents in this category include diazepam, lorazepam, alprazolam, triazolam, and estazolam. Triazolam's half-life of two to three hours is the shortest in this category, with the others ranging from eight to thirty hours. As a result of their short acting half-lives, the absorption, attainment of peak concentrations and onset of action are quickest. For long acting agents such as diazepam, chlordiazepoxide, clonazepam, clonazepam, flurazepam, prazepam, quazepam, and halazepam, half-lives are 30 to more than 100 hours in duration.<sup>7</sup> See Chart A for an overview of the pharmacokinetics of benzodiazepines.<sup>8</sup>

## CAUTIONS WITH LONG TERM USE OF BENZODIAZEPINES

Benzodiazepines have been shown to be effective in the short-term management of anxiety, but have not been effective in producing long-term improvement.<sup>9</sup> According to the National Institute for Health and Clinical Excellence (NICE), benzodiazepines can be used in the acute setting of anxiety, however they should not be used for longer than two to four weeks.<sup>10</sup>

Several cautions should not be overlooked in order to consider benzodiazepines for long-term anxiety therapy. Since the medication is metabolized by the liver, elderly and liver disease patients may need to be closely monitored through liver function testing. Caution should also be used in the treatment of obstetric patients. As there is potential for habit formation, benzodiazepines can be misused by polysubstance abusers who prefer agents with rapid peak drug effects such as diazepam, lorazepam, and alprazolam. And, since benzodiazepines have more of a sedating effect with longer half-lives, methadone users may take a benzodiazepine to augment a high while users of opiates may use benzodiazepines to self-medicate withdrawal symptoms. By raising the seizure threshold, benzodiazepines can also diminish the therapeutic effects of electroconvulsive therapy. Finally, considerable attention should be given to patient education of benzodiazepines leading to excessive sedation and respiratory depression when given with other CNS depressants such as alcohol, barbiturates, tricyclic and tetracyclic drugs, dopamine receptor antagonists, opioids, and antihistamines.

## USE IN PEDIATRICS

The role of long-term treatment with benzodiazepine category medications needs to be looked at from a patient perspective in

order to minimize complications. In the pediatric population, the drug is metabolized faster than in adults, thus children may require small divided doses to maintain blood level.<sup>11</sup> Adverse effects include sedation, cognitive, and motor effects, while disinhibition and agitation are reported in up to 30% of children.<sup>12</sup>

### USE IN GERIATRICS

In the geriatric population, specific caution should be used as drugs metabolized by oxidation can accumulate, while benzodiazepines combined with other drugs that affect the CNS may affect gait, memory, balance, cognition, behavior, fall risk, and motor vehicle collision risk.<sup>13</sup>

Benzodiazepines are often prescribed for the elderly population to treat symptoms of generalized anxiety disorder (GAD), agitation, alcohol withdrawal and insomnia. However, associated side effects are frequent and include intellectual, cognitive and psychomotor impairment, as well as an increased for falls and automobile accidents. Additionally, several studies indicated an association between benzodiazepine use with recurrent falls and hip fracture.

The risk of falls has been linked with sudden increases in dosage, as well as with continuous use of benzodiazepines. Consequently, benzodiazepines with shorter half-lives are recommended for the elderly to prevent accumulation of active metabolites in the blood. However, this approach brings with it a greater potential for abuse and dependence. A meta-analysis revealed the use of benzodiazepines in the elderly was associated with a 2.45 greater risk of developing adverse effects compared with placebo. In fact, for every seven elderly patients treated with a benzodiazepine, one will have an adverse event. Consequently, the use and potential side effects of benzodiazepine category medications in the elderly need to be closely monitored.<sup>14-18</sup>

### USE DURING PREGNANCY

The United States Food and Drug Administration (FDA) classifies benzodiazepines as pregnancy category “D”. Yet, in spite of these risks, the incidence of the use of benzodiazepines during pregnancy ranges from 1-40%. Animal studies demonstrate that benzodiazepines can interfere with fetal development, including neurodevelopment. The potential side effects during pregnancy include low birth weight, respirator and feeding difficulty, irritability, convulsions, floppy baby syndrome, neonatal drowsiness, hypotonia and withdrawal symptoms.<sup>19-22</sup>

Finally, in pregnant patients, benzodiazepines may cross the placenta and accumulate in the fetal circulation. In the third trimester, high doses may lead to fetal benzodiazepine

syndrome including floppy infant syndrome, impaired temperature regulation, and withdrawal symptoms. The threat to newborns in the benzodiazepine-dependent mother includes sedation, lethargy, and poor temperature regulation as benzodiazepines are excreted into breast milk in sufficient levels.<sup>23</sup> Longer acting agents can also accumulate in infants as the metabolism of benzodiazepines is slower in this population.<sup>24</sup>

### CAUTIONS WITH CHRONIC USE OF BENZODIAZEPINES

Chronic use of benzodiazepines has been associated with cognitive impairment, decreased motor coordination, impaired concentration, poor reaction time, and slower speed of information processing and verbal learning.<sup>25</sup> Patients on long-term benzodiazepines experience agoraphobia, loss of sex drive, social phobia, increased anxiety and depression, as well as various other problems. Learning impairment with benzodiazepines decreases the effect of psychotherapy.<sup>26</sup> In patients who have taken benzodiazepines regularly for one year, deficits in visual-spatial ability and sustained attention have been reported.<sup>27</sup> Excessive parenteral dosage can result in respiratory distress and apnea, along with a tranquilizing effect on the central nervous system.

Long-term benzodiazepine use puts patients at risk for dependence and withdrawal.<sup>28</sup> The most significant problems with chronic use of benzodiazepines are the development of tolerance and dependence. After four to eight months of treatment, as many as 40% of patients become dependent which explains why patients with substance abuse histories should not be prescribed benzodiazepines.<sup>29</sup> Additionally, withdrawal symptoms are possible after only one month of daily use, with up to 30% of patients suggested to experience withdrawal after eight weeks of benzodiazepine treatment.<sup>30</sup> In a meta-analysis study looking at withdrawal from an average of 17 mg per day of diazepam, the long term use of benzodiazepines has been shown to lead to substantial cognitive decline that did not resolve after three months of discontinuation.<sup>31</sup>

### GOALS OF BENZODIAZEPINE THERAPY

While benzodiazepines may be effective for the short-term treatment of generalized anxiety, more research is needed to better understand the effects of long term benzodiazepine therapy. As previously mentioned, placebo controlled trials of long term benzodiazepine therapy are not common due to their ethical concerns. If there is to be a role for long-term benzodiazepine therapy, patients and clinicians should be aware of the clinical effects due to the differences between long half-life and short half-life drugs. Advantages of long half-life benzodiazepines include less frequent dosing, less

variation in plasma concentration, and less severe withdrawal phenomena. Disadvantages of long half-life benzodiazepines include drug accumulation, increased risk of daytime psychomotor impairment and increased daytime sedation. For short half-life benzodiazepines, advantages include no drug accumulation and less daytime sedation. Disadvantages of short half-life benzodiazepines include more frequent dosing as well as earlier and more severe withdrawal syndromes, in addition to the more common symptoms of rebound insomnia and anterograde amnesia.<sup>32</sup>

### DISCONTINUATION OF BENZODIAZEPINE THERAPY:

As patients may become accustomed to using benzodiazepines for two months or more at a therapeutic dose, understanding withdrawal symptoms helps to optimize patient outcome. Benzodiazepines are known to produce withdrawal symptoms within one to two days following discontinuation of short acting drugs and within five to 10 days after discontinuation of long acting drugs.<sup>33</sup> Symptoms such as insomnia, agitation, anxiety, perceptual changes, dysphoria, headache, muscle aches, twitches, tremors, loss of appetite, gastrointestinal distress, and severe reactions such as seizures, coma, and psychotic states may prompt a clinician to suspect withdrawal.<sup>34</sup>

Current recommendations to discontinue benzodiazepine therapy to eliminate the potential for withdrawal symptoms includes substituting the current benzodiazepine with an equivalent dose of diazepam as well as:

1. Reduction of the total daily dosage of diazepam by 10 mg daily until a total dose of 20 mg is reached, then reducing the dose by five mg daily to an end point of abstinence, while possibly using propranolol to aid with withdrawal symptoms or
2. Reduction of the diazepam dosage by 25% per week, or
3. Reduction of the diazepam dosage by 50% over four to eight weeks, then tapering the final 50% of the dose more gradually. Notably, this protocol should not be used for alprazolam which must be decreased by 0.5 mg weekly as quicker discontinuation may lead to delirium and seizures.

Additionally, the use of carbamazepine (Tegretol) during benzodiazepine discontinuation has been reported to allow a better tolerated discontinuation when used at 400 to 500mg per day.<sup>35</sup>

### THE FUTURE ROLE OF LONG TERM BENZODIAZEPINES FOR ANXIETY:

With little data to support the long term use of benzodiazepines for anxiety, along with clinical studies that indicate cognitive impairment from prolonged use, a closer look should be taken to better understand why patients are prescribed benzodiazepines for greater than two months duration of treatment. Are patients being prescribed benzodiazepines as a result of poor clinical judgment, patient addiction, fear of withdrawal symptoms, or because clinicians don't understand how to best discontinue long term therapy?

As the diagnosis of generalized anxiety disorder requires a period of symptoms lasting greater than six months in duration, the clinician needs to take particular precaution not to overprescribe benzodiazepines as a short-term solution to an often long term problem. This is especially important as the most successful treatment solutions to GAD requires additional modalities that include lifestyle modifications, counseling, and/or psychotherapy.<sup>36</sup> As benzodiazepines have addiction potential and may be taken with other drugs of abuse to cause life-threatening complications or withdrawal symptoms, antidepressants may be the better pharmacologic option for the initial medical treatment of GAD.

## Addendum: Chart A

Generic Benzodiazepine	Brand Equivalent	Equiv Dose (mg)	Peak Plasma Level (PO)	Lipid Solubility	Elimination Half-Life	Metabolites	Comments	Use in Renal and Hepatic Disorders
Alprazolam	Xanax; Kalma; Apo-Alpraz; Novo-Aloprazol; Nu-Alprax; Tafil	0.5	1-2 h	Moderate	6-27 h	Metabolized by oxidation: principal metabolites are $\alpha$ -hydroxyalprazolam, desmethylalprazolam, 4-hydroxyalprazolam; Metabolized by CYP3A4 and 1A2	Rapidly and completely absorbed. Clearance in elderly only 50-80% that of young adults	Renal – increased plasma level of free unbound form and possible decreased clearance Hepatic – half-life increased
Bromazepam	Lexotan; Lexomil	3.0	0.5-4 h (2-12 h in elderly)	Low	8-30 h	Metabolized by oxidation: 3-hydroxybromazepam Metabolized by CYP3A4 In elderly peak plasma level and half-life increased	In elderly peak plasma level and half-life increased	?
Chlor-diazepoxide	Librium; Nova-Pam; Apo-chlordiazepoxide; Corax; Medilium; Novo-Poxide; Solium	25.0	1-4 h	Moderate	4-29 h (parent drug), 28-100 h (metabolites)	Metabolized by oxidation: desmethylchlordiazepoxide, oxazepam, desmethyl diazepam	Metabolites accumulate on chronic dosing	Renal – decrease dose by 50% in patients with creatinine clearance less than 10 mL/min Hepatic – half-life increased (2-3 fold) in patients with cirrhosis
Clonazepam	Klonopin; Rivotril	0.25	1-4 h	Low	19-60 h	Metabolized by oxidation: no active metabolite Metabolized primarily by CYP2B4, 2E1, and 3A4	Quickly and completely absorbed; slow onset of activity	Renal – no change Hepatic – increase in unbound clonazepam in patients with cirrhosis
Clorazepate Dipotassium	Gen-Xene; Tranxene; Apo-Clorazepate; Novo-Clopatate	10.0	0.5-2 h	High	1.3-120 h (metabolites)	Metabolized by oxidation: N-desmethyldiazepam	Metabolites accumulate on chronic dosing	Renal – clearance of metabolite impaired Hepatic - ?
Diazepam	Valium; Ducene; Antenex; D-Pam; Pro-Pam; Apo-Diazepam; Diazemuls; E Pam; Meval; Novo-Dipam; PMS-Diazepam; Vivol	5	1-2 h	High	14-80 h (parent drug) 30-200 h metabolites	Metabolized by oxidation: N-desmethyldiazepam, oxazepam, 3-hydroxydiazepam, temazepam Metabolized by CYP3A4, 2C9, 2C19, and 2B6 Inhibitor of UGT2B7	Less protein bound in elderly, attains higher serum levels; Rapid onset of action followed by re-distribution in adipose tissue; accumulation on chronic dosing	Renal – increased plasma level of unbound diazepam and decreased clearance Hepatic – 2-3 fold increase in half-life in patients with cirrhosis
Estazolam	ProSom; Tasedan	1	0.5-6 h	Low	8-24 h	Metabolized by oxidation: 4-hydroxyestazolam, 1-oxoestazolam Metabolized by CYP3A4	Metabolites inactive Metabolites impaired in the elderly and in hepatic disease	Renal - ? Hepatic – metabolism impaired
Flurazepam	Dalmane; Apo-Flurazepam; Novo-Flupam; PMS-Flupam; Somnol; Som Pam	15	0.5-1 h	High	0.3-3 h (parent drug) 40-250 h (metabolites)	Metabolized by oxidation: N-desalkylflurazepam, OH-ethylflurazepam, flurazepam aldehyde Metabolized by CYP2C and 2D6	Rapidly metabolized to active metabolite Elderly males accumulate metabolite more than young males on chronic dosing	Renal - ? Hepatic – metabolism impaired
Lorazepam	Ativan; Apo-Lorazepam; Novo-Lorazepam; Nu-Loraz; PMS-Lorazepam; Pro-Lorazepam	1	PO: 1-6h IM: 45-75 min IV: 5-10 min SL: 60 min	Moderate	8-24 h	Conjugated to form lorazepam glucuronide by UGT2B7	Metabolite not pharmacologically active	Renal – half-life of metabolite Increased Hepatic – half-life and volume of distribution doubled in patients with cirrhosis



Generic Benzodiazepine	Brand Equivalent	Equip Dose (mg)	Peak Plasma Level (PO)	Lipid Solubility	Elimination Half-Life	Metabolites	Comments	Use in Renal and Hepatic Disorders
Midazolam	Versed; Hypnovel; Dormicum	Acute use only	0.5-1 min	High	1-4 h (parent) 1-20 h metabolites	Metabolized by oxidation: 1-OH-methylmidazolam Metabolized primarily by CYP3A4	Metabolites active	Renal – decrease dose by 50% in patients with creatinine clearance less than 10 mL/min Hepatic – metabolism significantly impaired in patients with cirrhosis
Nitrazepam	Mogadon; Alodorm; Insoma; Nitrados	2.5	0.5-7 h	Low	15-48 h	Metabolized by nitroreduction by CYP2E1 No active metabolites	Metabolism impaired in elderly Accumulates with chronic use	Renal - ? Hepatic – metabolism impaired
Oxazepam	Serax; Serepax; Murelax; Aleпам; Serenid; Benzotran; Apo-Oxazepam; Novo-Oxazepam; Oxпам; PMS-Oxazepam; Zapex	15	1-4 h	Low	3-25 h	Conjugated to oxazepam glucuronide by UGT2B7	Metabolites not pharmacologically active Half-life and plasma clearance not affected much by age or sex	Renal – prolonged half-life Hepatic – no effect
Quazepam	Doral	7.5	1.5 h	High	15-40 h (parent) 39-120 h (metabolites)	Metabolized by oxidation: 2-oxoquazepam, Desalkylflurazepam Metabolized primarily by CYP2D6	Rapidly absorbed and metabolized Accumulation on chronic dosing	?
Temazepam	Restoril; Euhypnos; Normison; Temaze; Euhypnos; Nocturne; Normison; Temaze; Temtabs; Sompam	10	2.5 h	Moderate	3-25 h	Conjugated by UGT2B7	No accumulation with chronic use	Renal - ? Hepatic – no effect
Triazolam	Halcion; Apo-Triazo; Gen-Triazolam; Novo-Triolam; Nu-Triazo; Hypam; Tricam	0.25	1-2 h	Moderate	1.5-5 h	Metabolized by oxidation: 7- $\alpha$ -hydroxyderivative Metabolized by CYP3A4	Metabolite inactive; Clearance in elderly only 50-80% that of young adults	Renal – no change Hepatic – reduced clearance

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