Drug Class Review

Benzodiazepines in the Treatment of Anxiety Disorder

28:24.08 Benzodiazepines

Alprazolam (Xanax®)
Amitriptyline/Chlordiazepoxide (Limbitrol®)
Chlordiazepoxide (Librium®, others)
Clonazepam (Klonopin®)
Clorazepate (Traxene®, others)
Diazepam (Valium®, others)
Lorazepam (Ativan®)
Oxazepam (Serax®)

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Table of Contents:

Executive Summary

Introduction: Fourteen benzodiazepine agents are currently available for use in the United States: alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam and triazolam. Benzodiazepines are referred to as sedative-hypnotic agents and have a number of different therapeutic uses including treatment of anxiety disorders, insomnia, seizure disorders, alcohol withdrawal symptoms and for conscious sedation or general anesthesia. This review focuses on benzodiazepines in the treatment of anxiety disorders. Seven of the 14 available benzodiazepines are approved for the treatment of anxiety: alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, lorazepam and oxazepam. Chlordiazepoxide is also available in combination with a tricyclic antidepressant, amitriptyline.

In the United States, more than 15.7 million people suffer from an anxiety disorder alone, while an additional 11.7 million experience both anxiety and at least one other psychiatric disorder. It is estimated the annual cost of the anxiety disorders in the US was $42.3 billion in 1990 and this number has only continued to grow. The medical management of the anxiety disorders includes both pharmacotherapy and psychotherapy. A number of pharmacotherapy options exist for treatment of the anxiety disorders including: tricyclic antidepressants, monoamine oxidase inhibitors, second-generation antidepressants, anticonvulsants, antipsychotic medications, buspirone and benzodiazepines. Current guidelines recommend using a second generation antidepressant as first-line therapy in the treatment of anxiety disorders and benzodiazepines in treatment-resistant patients only as needed, on a short-term basis and only in patients without a history of substance abuse.

Clinical Efficacy: Clinical experience with benzodiazepines in treating patients with anxiety is examined in a number of review, experimental and observational trials. In the treatment of anxiety, the benzodiazepines were compared in one systematic review and eleven comparative efficacy trials. Overall, outcome measures were similar between each of the benzodiazepines evaluated in the treatment of anxiety disorders. The majority of available evidence is captured in nine clinical trials comparing alprazolam to other benzodiazepines. Although some psychometric assessments were more improved for diazepam when compared to alprazolam and clorazepate, total scores for the outcome measures exhibited no differences between treatment groups. Overall, improvements in anxiety outcome measures between alprazolam, clorazepate, diazepam, lorazepam and oxazepam in current literature are similar.

Special Populations: Benzodiazepines were evaluated in two special populations: geriatric patients and patients with a history of substance abuse. Evidence is limited and inconsistent regarding benzodiazepine use in these populations. It is recommended benzodiazepine use be limited in these populations and used only when necessary.

Adverse Drug Reactions: The benzodiazepines are generally well tolerated by patients with anxiety disorders. The most common drug-related adverse reactions are related to the sedative effects of the medication class. Evidence available for differences in adverse event rates between the benzodiazepine agents is limited. The benzodiazepines have varying pharmacokinetic

profiles which may contribute to differences in adverse event rates. Rapidly absorbed benzodiazepine agents have the most rapid onset of action but also the greatest abuse/dependence potential. Long-acting benzodiazepine agents are associated with accumulation which may result in sedation, cognitive impairment and psychomotor retardation. Short-acting benzodiazepine agents are associated with increased anxiety, insomnia and rebound effects upon discontinuation. All benzodiazepine agents are associated with dependence or tolerance with long-term use. Benzodiazepine therapy should be discontinued by a slow taper to avoid withdrawal effects. Adverse events may be reduced by using the smallest dose and shortest duration possible and by titrating the dose gradually.

Summary: Benzodiazepines are commonly used in the treatment of anxiety despite lack of widespread clinical evidence supporting their use. Clinical guidelines do not recommend benzodiazepines as first-line treatment of anxiety disorders. The majority of published clinical data available suggest similar outcomes and symptom reduction with the available benzodiazepines when used in the treatment of the anxiety disorders. Benzodiazepines have similar adverse events but the rates of these events may differ depending on individual pharmacokinetic profiles. Overall, benzodiazepines should be used at the lowest effective dose for the shortest duration possible with a comprehensive treatment plan and careful follow-up.

Introduction

A number of pharmacologic agents belong to the drug class referred to as sedative-hypnotic agents. Sedative-hypnotic agents work to induce a calming or sedating effect by depressing the central nervous system (CNS).[1] Sedative-hypnotic agents available in the United States include benzodiazepines, barbiturates and some newer anti-insomnia agents with unique chemical structures. This review focuses on benzodiazepines. Fourteen oral and parenteral benzodiazepine agents are currently available for use in the United States: alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam and triazolam.[2] Chlordiazepoxide is also available in two combination products: chlordiazepoxide/amitriptyline and clidinium-chlordiazepoxide.[2] Alprazolam is also available in an extended release formulation.[2] Table 1 compares all of the benzodiazepine agents.

Benzodiazepines have been used therapeutically since the early 1950s and were initially apart of a class of therapeutic agents referred to as tranquilizers.[3] The "new" benzodiazepine agents were safer than the older barbiturate agents with far less addiction potential. Presently, benzodiazepines are referred to as sedative-hypnotic agents and have a number of different therapeutic uses including treatment of anxiety disorders, insomnia, seizure disorders, alcohol withdrawal symptoms and for conscious sedation or general anesthesia.[1-3] This review will focus on benzodiazepines in the treatment of anxiety disorders. Seven of the 14 available benzodiazepines are approved for the treatment of anxiety: alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, lorazepam and oxazepam. Chlordiazepoxide, also available in combination with a tricyclic antidepressant, amitriptyline, is used in the treatment of anxiety and will be covered in this review.

Research into benzodiazepine mechanism of action and therapeutic use continues to be very active and has led to various modifications of the basic structure.[3] Newer insomnia drugs, namely the benzodiazepine receptor agonists, are a result of this continued research and development. Currently, benzodiazepines account for about one out of every five controlled substance prescriptions in the United States. In 2006, benzodiazepines were the tenth most frequently prescribed therapeutic class in the United States, with over 80 million prescriptions dispensed.[4]

Table 1. Comparison of Benzodiazepine Agents[1,2,5,6]

Product	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Active Metabolite	Generic Available
Alprazolam (Xanax® and Xanax XR®)	Oral	Oral tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg 0.5 mg XR, 1 mg XR, 2 mg XR, 3 mg XR Oral solution: 1mg/mL (30 mL)	Treatment of anxiety disorders, panic disorder and anxiety associated with depression.	Treatment of anxiety in children.	No	Yes
Chlordiazepoxide (Librium®, others)	Oral, IM, IV	Oral tablets: 5 mg, 10 mg, 25 mg	Treatment of anxiety disorders, withdrawal symptoms of acute alcoholism and preoperative apprehension/anxiety.	N/A	Yes	Yes
Chlordiazepoxide/Amitriptyline (Limbitrol®)	Oral	5/12.5 mg, 10/25 mg	Treatment of anxiety, agitation and depression.	N/A	Yes	Yes
Clidinium/Chlordiazepoxide (Librax®)	Oral	2.5/5 mg	Treatment of irritable bowel syndrome and adjunct treatment of peptic ulcer.	N/A	Yes	Yes
Clobazam (Onfi™)	Oral	5 mg, 10 mg, 20 mg	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome	Catamenial epilepsy; epilepsy (monotherapy)	Yes	No
Clonazepam (Klonopin®)	Oral	0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg	Treatment of petit mal variant (Lennox-Gastaut), akinetic and myoclonic seizures; petit mal (absence) seizures unresponsive to succimides; and panic disorder.	Treatment of restless leg syndrome, neuralgia, multifocal tic disorder, parkinsonian dysarthria, bipolar disorder, burning mouth syndrome and adjunct therapy for schizophrenia.	No	Yes
Clorazepate (Traxene®, others)	Oral	3.75 mg, 7.5 mg, 15 mg	Treatment of anxiety disorders, ethanol withdrawal and adjunct in management of partial seizures.	N/A	Yes	Yes
Diazepam (Valium®, others)	Oral, IM, IV, Rectal	Oral tablets: 2 mg, 5 mg, 10 mg Oral solution: 1mg/mL (5 mL, 500 mL), 5mg/mL (30 mL) Injection solution: 5mg/mL (2 mL, 10 mL) Rectal Gel: 5 mg, 10 mg, 20 mg	Oral and injection: Treatment of anxiety disorders, ethanol withdrawal, skeletal muscle relaxant, convulsive disorders and sedation/amnesia. Rectal gel: Treatment of refractory epilepsy patients.	Treatment of panic disorders and spasticity in children with cerebral palsy.	Yes	Yes
Estazolam (Prosom®)	Oral	1 mg, 2 mg	Short-term treatment of insomnia.	N/A	No	Yes
Flurazepam (Dalmane®)	Oral	15 mg, 30 mg	Short-term treatment of insomnia.	N/A	Yes	Yes

Product	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Active Metabolite	Generic Available
Lorazepam (Ativan®)	Oral, IM, IV	Oral tablets: 0.5 mg, 1 mg, 2 mg Oral solution: 2mg/mL (30 mL) Injection solution: 2mg/mL (1 mL, 10 mL), 4mg/mL (1mL, 10 mL)	Oral: Treatment of anxiety disorders and short-term management of anxiety associated with depressive symptoms. I.V.: Status epilepticus, amnesia and sedation.	Treatment of ethanol withdrawal, insomnia, psychogenic catatonia, partial complex seizures, agitation and as antiemetic adjunct.	No	Yes
Midazolam (Versed®)	Oral, IV, IM	Oral solution: 2mg/mL (118 mL) Injection solution: 1mg/mL (2 mL, 5 mL, 10 mL), 5mg/mL (1 mL, 2 mL, 5 mL, 10 mL)	For preoperative, preprocedural, or ICU sedation and induction/maintenance of general anesthesia.	Treatment of anxiety and status epilepticus.	Yes	Yes
Oxazepam (Serax®)	Oral	10 mg, 15 mg, 30 mg	Treatment of anxiety and ethanol withdrawal.	Management of simple partial seizures and as a hypnotic.	No	Yes
Quazepam (Doral®)	Oral	15 mg	Treatment of insomnia.	N/A	Yes	No
Temazepam (Restoril®)	Oral	7.5 mg, 15 mg, 22.5 mg, 30 mg	Short-term treatment of insomnia.	Treatment of anxiety, panic attacks and as an adjunct in the treatment of depression.	No	Yes; excluding 7.5 mg and 22.5 mg doses
Triazolam (Halcion®)	Oral	0.125 mg, 0.25 mg	Short-term treatment of insomnia.	N/A	No	Yes

Key: IM = intramuscular, IV = intravenous

Disease Overview

The DSM (Diagnostic and Statistical Manual of Mental Disorders) classification is the 5-axis diagnostic system developed and published by the American Psychiatric Association (APA). The DSM multi-axial system provides a comprehensive and systematic evaluation of the patient to identify and diagnose mental health disorders.[7,8] The axis I DSM psychiatric disorders include the depressive and anxiety disorders. Numerous anxiety disorders are included in this category including: acute stress disorder, agoraphobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder and posttraumatic stress disorder (PTSD).[7,8] The anxiety disorders are the most common outpatient psychiatric illnesses and up to 75% of patients who have experienced a panic attack will meet the diagnosis for a major depressive disorder. It is estimated the annual cost of the anxiety disorders in the US was $42.3 billion in 1990.[9,10] This included costs due to nonpsychiatric medical treatment, psychiatric treatment, lost productivity and prescription costs. Alcohol and/or substance abuse problems may also occur in patients with anxiety disorders, as a form of self-medication.[11-16] The costs associated with anxiety disorders may be avoided with increased awareness, education and early recognition and treatment.

The medical management of the anxiety disorders includes both pharmacotherapy and psychotherapy. With regard to psychological therapies, cognitive-behavioral therapy (CBT) is considered the gold standard.[17,18] A number of pharmacotherapy options exist for treatment of the anxiety disorders including: tricyclic antidepressants, monoamine oxidase inhibitors, second-generation antidepressants, anticonvulsants, antipsychotic medications, buspirone and benzodiazepines. Historically, the benzodiazepines were the core of the medical management of anxiety disorders due to their tolerability and rapid onset of action.[18] A short course of a benzodiazepine, at the lowest dose and only on an as-needed basis, is the usual recommendation for benzodiazepine therapy in the treatment of anxiety disorders. Buspirone, an anxiolytic, may be effective in the treatment of generalized anxiety disorders, is dosed multiple times a day and requires several weeks of therapy before a response is seen.[11] The second-generation antidepressants, including escitalopram, paroxetine, venlafaxine and duloxetine, are labeled for use in GAD and may be safer options for the long-term treatment of chronic anxiety. Other agents used in the treatment of anxiety include the GABA-nergic acting anticonvulsants, divalproex, gabapentin, oxcarbazepine, pregabalin and tiagabine.[11] Overall, choice of therapy is based on presenting anxiety disorder, patient history and medical costs. The combination of both pharmacotherapy and psychotherapy is beneficial in the treatment of all anxiety disorders.[17,18]

Current guidelines from the World Federation of Societies of Biological Psychiatry (2012)[19] recommend using a second generation antidepressant as first-line therapy in the treatment of anxiety disorders because they are effective and well-tolerated. According to the guidelines, benzodiazepines should only be used in treatment-resistant patients without a history of substance abuse.[19] The most current recommendations from the World Council of Anxiety (2003)[20-25] also support the use of second generation antidepressants as first-line therapy in the treatment of anxiety

disorders. According to the World Council of Anxiety, benzodiazepines may be beneficial in the short-term treatment of anxiety disorders but their adverse-effect profiles limit use in the long-term treatment of anxiety disorders.[20-25] In general, short-term is defined as ≤ 4 months. The APA has published individual practice guidelines with recommendations for each of the individual anxiety disorders.[26-28] Overall, the APA recommends using a second generation antidepressant as first-line therapy for the treatment of PTSD, OCD or panic disorder. Benzodiazepines are recommended only as add-on therapy for patients who are treatment-resistant to first-line treatment.[26-28] Guidelines from the American Academy of Child and Adolescent Psychiatry recommend treatment with a second-generation antidepressant if CBT is unsuccessful in the treatment of OCD in pediatric patients (2012).[29] Two National Institute for Health and Care Excellence (NICE) guidelines are available: one addressing the management of general anxiety and panic disorders in adults[13] and one developed by the National Collaborating Centre for Mental Health on behalf of NICE addressing social anxiety disorder.[14] Both guidelines recommend the second-generation antidepressant agents for first-line pharmacologic treatment. According to the guidelines, benzodiazepines should only be used short-term in general anxiety and panic disorders and should not be used in social anxiety disorder. Table 2 summarizes the current clinical practice guidelines available for the treatment of anxiety disorders.

Table 2. Current Clinical Guidelines for the Treatment of Anxiety Disorders

Guideline	Recommendations
Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care; World Federation of Societies of Biological Psychiatry (2012)[19]	First-line pharmacological treatments • selective serotonin reuptake inhibitors for all anxiety disorders • serotonin-norepinephrine reuptake inhibitors in GAD, panic disorder, agoraphobia • pregabalin for generalized anxiety disorder only Combination of medication and cognitive behavior therapy is the clinically desired treatment strategy. Benzodiazepines should be used as needed and short-term, in addition to a regular pharmacological treatment regimen. Of note, benzodiazepines were not found to be effective in acute stress disorder and in conditions with depression comorbidity or OCD.
Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder; American Academy of Child and Adolescent Psychiatry (2012)[29]	When possible, CBT is the first line treatment for mild to moderate cases of OCD in children. For moderate to severe OCD, medication is indicated in addition to CBT. Serotonin reuptake inhibitors (SRIs) are the first-line medications recommended for OCD in children and should be monitored closely for response, tolerability and safety.
NICE: Generalized anxiety disorder and panic disorder in adults: management. [CG113][13]	First-line: • Choice of high-intensity psychological intervention (cognitive behavior therapy (CBT) or applied relaxation or drug treatment • Psychological Intervention: 12 to 15 1-hour sessions of psychological intervention • Pharmacological Treatment: Selective serotonin reuptake inhibitor (SSRI)

	Second-line: • A second SSRI or serotonin/norepinephrine reuptake inhibitor (SNRI) • If unable to tolerate SSRI/SNRI, consider pregabalin • ONLY use benzodiazepine short-term • Do NOT use antipsychotics for GAD

NICE: Social anxiety disorder: recognition, assessment and treatment NICE guidelines [CG159], 2013[14]	Interventions:
	• Cognitive behavioral therapy (CBT). Promote CBT before pharmacological therapy.
	• For Partial Response to CBT, consider combination of drug therapy and CBT
	  ○ Pharmacologic therapy: selective serotonin reuptake inhibitor (SSRI) such as escitalopram or sertraline.
	• For Partial Response to Drug Therapy (after 12 weeks) or Side Effects:
	  ○ Alternative SSRI (fluvoxamine or paroxetine) or serotonin/norepinephrine reuptake inhibitor (SNRI), such as venlafaxine
	  ○ Monoamine oxidase inhibitor (MAOI) such as phenylzine or moclobemide
	
	NOT recommended: pharmacological interventions including anticonvulsants, tricyclic antidepressants, benzodiazepines, or antipsychotic medication, St. John's wort or other over-the-counter preparations

Treatment of Patients With Acute Stress Disorder and Posttraumatic Stress Disorder, APA (2004)[26]	Treatment of ASD or PTSD symptoms includes three broad categories of intervention: pharmacological treatment, psychotherapeutic intervention and education and supportive measures. SSRIs are recommended as first-line medication treatment for PTSD. Other antidepressants (Tricyclic antidepressants and MAOIs) and benzodiazepines may also be beneficial as second-line or add-on options.
Practice guideline for the treatment of patients with obsessive-compulsive disorder, APA (2007)[27]	CBT and SSRIs are recommended on the basis of clinical trial results as safe and effective first-line treatments for OCD; "Clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline, which are approved by the FDA for treatment of OCD, are recommended pharmacological agents." Strategies for Moderate Response: Augment with a second-generation antipsychotic or with CBT, if not already provided. Strategies for Little or No Response: Switch to a different SSRI (may try more than one trial), switch to clomipramine, augment with a second-generation antipsychotic, switch to venlafaxine, switch to mirtazapine. Benzodiazepines cannot be recommended as monotherapy for OCD.
Practice guideline for the treatment of patients with panic disorder; APA (1998, update 2009)[28]	The use of an SSRI, SNRI, TCA, benzodiazepine (appropriate as a monotherapy only in the absence of a co-occurring mood disorder) or CBT as the initial treatment for panic disorder is strongly supported by demonstrated efficacy in numerous controlled trials.

Key: GAD=generalized anxiety disorder, SSRI=selective serotonin reuptake inhibitor, SNRI=selective serotonin/norepinephrine reuptake inhibitor, CBT=cognitive behavior therapy

Pharmacology

All benzodiazepine agents enhance the binding of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter, to the GABA-A subtype of GABA receptors, resulting in GABAergic neurotransmission.[5,6] All benzodiazepine agents exert similar clinical effects. However, differences in their pharmacokinetic profiles, such as rate of absorption, elimination half-life and lipid solubility, contribute to varying patterns of therapeutic application by influencing onset and duration of action.[5,6] Table 3 provides a summary of the pharmacokinetic properties for each of the benzodiazepine agents indicated in the treatment of the anxiety disorders.

Lorazepam, oxazepam and alprazolam have low hepatic metabolism and do not have active metabolites.[11,13,15,16,30,31] Diazepam and chlorazepate are rapidly absorbed benzodiazepine agents and have the most rapid onset of action but also the greatest abuse/dependence potential. Chlordiazepoxide, clonazepam, clorazepate and diazepam are considered long-acting benzodiazepine agents and are associated with accumulation which may result in sedation, cognitive impairment and psychomotor retardation. Alprazolam and lorazepam are considered short-acting benzodiazepine agents and have been associated with increased anxiety, insomnia and rebound effects upon discontinuation. All benzodiazepine agents result in dependence or tolerance with long-term use.[32,33] Benzodiazepine therapy should be discontinued by a slow taper to avoid withdrawal effects including: “sleep disturbance, irritability, increased tension and anxiety, panic attacks, hand tremor, sweating, difficulty in concentration, dry wretching and nausea, some weight loss, palpitations, headache, muscular pain” and may also include more serious effects including seizures and psychotic reactions.[34] Transitioning patients from long-acting to short-acting agents may allow for more flexibility and aid in discontinuing therapy.[11,13,15,16,30,31]

Table 3. Pharmacokinetics Properties of the Benzodiazepine Agents[1,2,5,6]

Product	Route of Administration	Absorption	Distribution	$t_{½}$, hours	Metabolism	Active Metabolite	Elimination
Alprazolam	Oral	Readily absorbed; Extended release: Slower relative to immediate release formulation resulting in a concentration that is maintained 5 to 11 hours after dosing; rate increased following night time dosing (versus morning dosing) Bioavailability: Immediate release: 84% to 92%; Extended release: 90%	Immediate release: Vd: 0.84 to 1.42 L/kg Protein binding: 80%; primarily to albumin	6.3-26.9	Hepatic via CYP3A4; forms two active metabolites (4-hydroxyalprazolam and α-hydroxyalprazolam [about half as active as alprazolam]) and an inactive metabolite benzophenone metabolite, however, the active metabolites are unlikely to contribute to much of the pharmacologic effects because of their low concentrations and lesser potencies.	No	Urine (as unchanged drug and metabolites)
Chlordiazepoxide	Oral, IM, IV	Well absorbed: peak concentrations 1-2 hours after administration; rate of absorption is age-related and tends to be delayed in the elderly.	Vd: 3.3 L/kg Protein binding: 96%	18-96	Extensively hepatic to desmethyldiazepam (active and long-acting), desmethylchlordiazepoxide, and demoxepam	Yes	Urine (minimal as unchanged drug)
Clonazepam	Oral	Rapidly and completely absorbed Onset of action: ~20 to 40 minutes Bioavailability: ~90%	Children: Vd: 1.5 to 3 L/kg; Adults: Vd: 1.5 to 64.4 L/kg Protein binding: ~85%	18-50	Extensively hepatic via glucuronide and sulfate conjugation; undergoes nitroreduction to 7-aminoclonazepam, followed by acetylation to 7-acetamidoclonazepam; nitroreduction and acetylation are via cytochrome P450 enzyme system; metabolites undergo glucuronide and sulfate conjugation	No	Urine (<2% as unchanged drug); metabolites excreted as glucuronide or sulfate conjugates
Clorazepate	Oral	Rapidly absorbed following oral administration Bioavailability: 91%	Nordiazepam: Vd: 0.7 to 2.2 L/kg Protein binding: Nordiazepam: 97% to 98%	40-120	Rapidly decarboxylated to nordiazepam (active) in acidic stomach prior to absorption; nordiazepam is hepatically hydroxylated by CYP 2C19 and CYP3A4 to oxazepam (active) and undergoes glucuronidation to form a glucuronide conjugate	Yes	Urine (62% to 67%; primarily metabolites of conjugated oxazepam); feces (15% to 19%)

Product	Route of Administration	Absorption	Distribution	$t_{½}$, hours	Metabolism	Active Metabolite	Elimination
Diazepam	Oral, IM, IV, Rectal	Oral: Well absorbed (>90%); delayed and decreased when administered with a moderate fat meal Rectal: Well absorbed Bioavailability: IM: >90% Oral: >90% Rectal: 90%	IV: 1.2 L/kg (range: 0.6 to 2 L/kg) Oral: 1.1 L/kg (range: 0.6 to 1.8 L/kg Rectal: 1 L/kg Protein binding: Oral: Neonates: 84% to 86% Adults: 98% Rectal: 95% to 98%	40-120[a]	Hepatic; diazepam is N-demethylated by CYP3A4 and 2C19 to the active metabolite N-desmethyldiazepam, and is hydroxylated by CYP3A4 to the active metabolite temazepam. N-desmethyldiazepam and temazepam are both further metabolized to oxazepam. Temazepam and oxazepam are largely eliminated by glucuronidation.	Yes	Urine (predominantly as glucuronide conjugates)
Lorazepam	Oral, IM, IV	IM: Rapid and complete absorption Oral: Readily absorbed Onset of action: Anticonvulsant: IV: Within 10 minutes Hypnosis: IM: 20 to 30 minutes Sedation: IV: Within 2 to 3 minutes Bioavailability: Oral: 90%	IV: Vd: Neonates: 0.76 ± 0.37 L/kg (range: 0.14 to 1.3 L/kg) Pediatric patients: Crosses the blood brain barrier 5 months to < 3 years: 1.62 L/kg (range: 0.67 to 3.4 L/kg) 3 to <13 years: 1.5 L/kg (range: 0.49 to 3 L/kg) 13 to <18 years: 1.27 L/kg (range: 1 to 1.54 L/kg) Adults: 1.3 L/kg Protein binding: ~85% to 93%; free fraction may be significantly higher in elderly	10-20	Hepatic; rapidly conjugated to lorazepam glucuronide (inactive)	No	Urine (~88%; predominantly as inactive metabolites); feces (~7%)
Oxazepam	Oral	Slowly absorbed from the GI tract	Vd: 0.6 to 2 L/kg Protein binding: 96% to 98%	5-20	Hepatic glucuronide conjugation to produce a single, major inactive metabolite (benzophenone)	No	Urine (as inactive glucuronide conjugate)

[a]Half-life of active metabolite, to which effects can be attributed. IM = intramuscular, IV = intravenous

Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database (1950 – 2016), the Cochrane Library and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed prior to 9/2016, evaluating efficacy of benzodiazepine agents in anxiety disorders with reduction of symptoms as the endpoint are included. Trials evaluating the benzodiazepines as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens are excluded. The following reports were excluded (note: some were excluded for more than 1 reason):

- Individual clinical trials which evaluated endpoints other than reduction of anxiety symptoms, such as discontinuation studies[35-38], mode-of-action/onset-of-action[39-41], drug plasma concentrations[42-44], methodology studies[45,46], cortisol response[47], memory and behavioral learning[48-51], quality of life[52], muscle sympathetic activity[53], kinetics[54,55], EEG changes[56-60] or other indications.[61-95]
- Individual trials comparing benzodiazepines in dose-finding studies[96,97] or in healthy volunteers.[44,55,90,97-108]
- Individual clinical trials evaluating benzodiazepine agents or formulations not currently available in the US[35,42,56,109-139 140] or clinical trials without access to the full article.[141-144]

Clinical Efficacy

Clinical experience with benzodiazepines in treating patients is examined in a number of review, experimental and observational trials. The Appendix summarizes all of the available clinical trials with benzodiazepines.

- **How do the benzodiazepines compare with each other for reducing anxiety symptoms?**

One systematic review was identified for evaluation of benzodiazepines in the treatment of anxiety.[145] Eleven comparative efficacy trials directly comparing at least two benzodiazepines were identified for evaluation.[146-155] The majority of the clinical efficacy data comes from trials evaluating alprazolam. Alprazolam was compared to lorazepam in three clinical trials[146,153,154], diazepam in two clinical trials[147,150] and oxazepam in two clinical trials.[152,155] Two study doses of alprazolam were compared in one clinical trial.[149] Two additional clinical trials, one comparing clorazepate to diazepam[148] and one comparing clorazepate to lorazepam[151], were also identified for evaluation. See Table 4 for a summary of the comparative effectiveness from clinical trials evaluating benzodiazepines in the treatment of anxiety. See Table 5 for an explanation of the most common outcome measures used to evaluate efficacy of benzodiazepines in treating anxiety.

Table 4. Comparative Effectiveness of Benzodiazepines in Outcome Measures for Anxiety in Clinical Trials.[146-155]

Agent	Change in Outcome Measures		Number of Clinical Trials
	Hamilton Anxiety Rating Scores	*Hopkins Anxiety Rating Scores*	
Alprazolam	8.9-12.1	0.69-1.49	9
Clorazepate	~9.5	N/A	2
Diazepam	7.21-11.2	0.52-1.53	3
Lorazepam	8.6-11.3	~5.1	4
Oxazepam	~14.6	N/A	2

Table 5: Scales used as Outcomes Measures in Benzodiazepine Trials Evaluating Efficacy in Anxiety.[156-161]

Measurement Scale	Description of scale	*Comments*
Hamilton Anxiety Rating Scale	Measures both psychic and somatic anxiety on a 56-point scale with a 14-item clinician-rated survey defined by a series of symptoms. An 18-20+ is a common index of severity required for entry into a clinical trial. A 40% to 50% reduction in the HAM-A total score (score of 8-10 or less) is a common index of treatment response.	May have poor ability to discriminate between anxiolytic and antidepressant effects and somatic anxiety versus somatic side effects.
Hopkins Anxiety Rating Scale	A 25-item self-report symptom scale, with each item scored on a Likert scale from 1 (not at all) to 4 (extremely). An average of scores is calculated and a cut-off point of 1.75 is generally accepted for diagnosis.	Originally developed as a self-report symptom inventory but can be used as an interviewer administered scale.
Profile of Mood States (POMS) tension-anxiety	A 9-item patient-report symptom scale, with each item scored on a Likert scale from 1 (not at all) to 4 (extremely).	The tension-anxiety POMS score is a subscore of the POMS 55-item, 6-state survey.
Global Impression Scores	A 3-item observer-rated scale that measures illness severity rated on a 7-point scale, from 1 (normal) to 7 (severely ill); global improvement or change rated on a 7-point scale, from 1 (very much improved) to 7 (very much worse); and therapeutic response.. rated on a 4-point scale, from 0 (marked improvement and no side-effects) to 4 (unchanged or worse and side-effects outweigh the therapeutic effects).	Each component of the Global Impression Score is rated separately; the instrument does not yield a total score.

The single systematic review identified for evaluation of benzodiazepines in the treatment of anxiety identified and compared 23 placebo-controlled trials with

alprazolam, diazepam, or lorazepam.[145] In total, Martin et al[145] evaluated 2,326 patients with general anxiety disorder enrolled in the 23 trials published from 1983-2003. Overall, the authors found evidence supporting the efficacy of benzodiazepine use in the treatment of GAD. Based on study withdrawal data, there were no significant differences between alprazolam, diazepam, or lorazepam in the treatment of general anxiety disorder. Overall, alprazolam had a slightly lower relative risk for withdrawal for any reason (0.58), followed by diazepam (0.80) and lorazepam (1.12).[145]

In each of the three clinical trials evaluating alprazolam compared to lorazepam, no differences in efficacy were found.[146,153,154] In each of the studies, Hamilton Anxiety Rating scores were improved when compared to placebo or baseline with no differences between treatment groups. There were also no statistically significant differences in safety between the two treatment groups. However, lorazepam tended to have higher overall rates of adverse events (including vertigo, nausea, asthenia and discontinuation due to adverse events) than alprazolam or placebo in each of the three trials.

In each of the two studies evaluating alprazolam compared to diazepam, outcome measures were similar between the treatment groups.[147,150] No differences in efficacy were found in the overall Hamilton Anxiety Rating scores, Hopkins Anxiety Rating scores, or in the physicians global rating scores between alprazolam and diazepam. One of the two studies found depressed mood scores were significantly more improved with diazepam when compare to alprazolam.[147] Elie et al[147] evaluated 48 patients with mild to moderate anxiety. Patients received treatment with either alprazolam or diazepam for 30 days. Outcome measures were assessed at four times throughout the study (weeks 0, 1, 2 and 4). At weeks 2 and 4, diazepam had significantly improved Hamilton Anxiety Rating scores when compared to alprazolam for lowering depressed mood (0.45 for diazepam vs. 0.83 for alprazolam week two; 0.33 for diazepam vs. 0.73 for alprazolam week four, $p < 0.05$).[147] Also of note, a significantly greater rate of sedation was reported with diazepam at week two (74%) when compared to alprazolam (48%, $p < 0.05$), although this difference was not demonstrated at any other time point during the study.[147] No other statistically significant differences in safety or the Hamilton Anxiety Rating scores were found between treatment groups.

In each of the two studies evaluating alprazolam compared to oxazepam, no differences in efficacy were found.[152,155] In each of the studies, Hamilton Anxiety Rating scores were improved when compared to baseline but there were no differences between treatment groups. Improvements were also seen in the Lipman Self-Rating scores and both objective and subjective Global Impression scores. There were no statistically significant differences in safety between the two treatment groups.[152,155]

In the single study comparing two doses of alprazolam no differences in efficacy were found between the treatment doses.[149] Lydiard et al[149], studied 94 patients with panic disorder for a total of 7 weeks (one week of placebo followed by six weeks of treatment). Patients received either 2 mg or 6 mg of alprazolam or placebo once daily for treatment of panic symptoms. Overall, fewer instances of panic attacks were noted with patients receiving alprazolam when compared to placebo but no differences in frequency

of panic attacks were found between the treatment groups. The higher dose of alprazolam was associated with increased rates of adverse events (including impaired coordination and slurred speech) but no significant differences in adverse events between the treatment groups were reported.

In each of the two studies evaluating clorazepate, outcome measures were similar between the treatment groups.[148,151] Clorazepate was compared to diazepam in one five-week trial (one week of placebo followed by 4-weeks of treatment) evaluating 30 outpatient adults with symptoms of anxiety.[148] Although some psychometric assessments were more improved for diazepam when compared to clorazepate, total scores for both the Hamilton Anxiety Rating scale and Wittenborn Psychiatric Rating scale exhibited no differences between treatment groups.

Clorazepate was compared to lorazepam in one seven-week trial (one week of placebo, 4-weeks of treatment and 2-week follow-up period) evaluating 62 adult patients with general anxiety disorder.[151] Overall, no differences in Hamilton Anxiety Rating scores, POMS Tension-Anxiety scores, or global impression scores were found between treatment groups. During week one of treatment, a significantly higher rate of adverse events were reported with lorazepam (43.3%) when compared to clorazepate (15.6%, $p < 0.05$). No differences in safety between treatment groups were found at any other time point during the seven-week trial.

In summary, the overall improvements in anxiety outcome measures between alprazolam, clorazepate, diazepam, lorazepam and oxazepam in current literature are similar. The majority of available evidence is captured in nine clinical trials comparing alprazolam to other benzodiazepines. Although some psychometric assessments were more improved for diazepam when compared to alprazolam and clorazepate, total scores for the outcome measures exhibited no differences between treatment groups. Overall, outcome measures were similar between each of the benzodiazepines evaluated in the treatment of anxiety disorders.

- **Are there patient subgroups based on demographics (e.g., age, racial groups, gender) or comorbidities for which one of the benzodiazepines is more effective or associated with fewer adverse effects?**

Geriatric Patients

There is limited evidence available comparing the benzodiazepines in geriatric patients. Benzodiazepine drug use is associated with increased risk for falls in older persons.[162] Approximately 30% of community-dwelling and 50% of nursing home adults older than 65 years of age fall every year.[162-164] Leipzig et al[162], conducted a systematic analysis of trials evaluating sedative/hypnotic, antidepressant, or neuroleptic drug use with falling in adults aged $\geq$60. A total of 40 trials were included in the analysis. Benzodiazepines were found to be associated with increased risk for falls but no statistically significant differences were reported between specific benzodiazepine agents

or between the short- and long-acting benzodiazepine agents. Overall, the data suggest all benzodiazepines should be used with caution in geriatric patients.[162-164]

Patients with a History of Drug/Alcohol Abuse

There is limited evidence available comparing the benzodiazepines in patients with a history of drug/alcohol abuse.[165,166] In two prospective studies, evidence was inconclusive regarding increased risk for abuse in this population.[167,168] One longitudinal study found former alcoholics may reduce benzodiazepine use over time.[169] Sokolow et al[169], followed a cohort of 1,340 patients with a history of alcohol abuse over 8 months. The authors concluded that patients with a history of alcohol abuse are not at higher risk for benzodiazepine abuse. A second study found no differences in benzodiazepine use between patients with a history of substance abuse and patients without a history of substance abuse.[170] Romach et al[170], evaluated 123 patients taking a benzodiazepine, of which 40% (n = 49) had a history of prior history of alcohol abuse or dependence. Overall, the patterns of benzodiazepine use by patients with a history of substance abuse did not indicate abuse, addiction, or drug dependence for any of the patients. Although there is limited evidence for benzodiazepine use in patients with a history of substance abuse, the majority of the data suggest benzodiazepines may still be used in this population with a comprehensive treatment plan and careful follow-up.[165,166]

Adverse Drug Reactions

- **How does the safety of the benzodiazepines compare with each other?**

The benzodiazepines are generally well tolerated in patients with anxiety disorders.[171,172] The most common drug-related adverse reactions to benzodiazepines include blurred vision, confusion, drowsiness, dizziness, decreased alertness or concentration, euphoria, lack of coordination, nausea, nightmares and sexual effects (decreased libido). Additionally, hypotension and suppressed breathing have been reported with intravenous use.[171,172] A number of the commonly cited adverse events for benzodiazepine agents cause overall psychomotor impairment and may result in increased risk for falls, injuries, or impairment of driving skills, particularly in the elderly or patients using more than one sedative-type drug.[171-174] Table 6 provides a summary of the warnings and precautions associated with benzodiazepine therapy and Table 7 lists the adverse events reported with each of the benzodiazepines.

Withdrawal symptoms may be precipitated with benzodiazepine discontinuation.[175] Withdrawal symptoms include anxiety and insomnia and may also include tinnitus, involuntary movements, perceptual changes, confusion and seizures. Withdrawal symptoms can be reduced by using the smallest dose and shortest duration possible and by tapering the dose gradually.[175]

Evidence on differences in adverse event rates between benzodiazepine agents is limited. Benzodiazepines differ in their pharmacokinetic profiles which can contribute to differences in adverse event rates.[171,172] For example, long-acting benzodiazepines can accumulate and lead to an increased risk of dizziness, confusion, hypotension, or cognitive impairment. Some benzodiazepines have active metabolites. Active metabolite accumulation may occur more frequently in the elderly because of slowed hepatic and renal metabolic activity and may also result in increased adverse events. Short-acting benzodiazepines are also associated with increased risks, including more intense withdrawal symptoms and rebound anxiety. See Table 3 for a complete review of half-life and active metabolites for all available benzodiazepines.

Table 7. Warnings and Precautions for the Benzodiazepine Agents[176,177]

Warnings	Precautions	Other Considerations
ALERT: US Boxed Warning Risks from concomitant use with opioids: Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation. Contraindications: Hypersensitivity to agent or any component of the formulation (cross-sensitivity with other benzodiazepines may exist).	Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties. Breakthrough anxiety: At the end of dosing interval, breakthrough anxiety may occur. Tolerance: Alprazolam has a short half-life for a benzodiazepine and the duration of action after a single dose is determined by redistribution rather than metabolism. Tolerance does not develop to the anxiolytic effects. Chronic use of this agent may increase the perioperative benzodiazepine dose needed to achieve desired effect. Withdrawal: Rebound or withdrawal symptoms, including seizures, may occur following abrupt discontinuation or large decreases in dose (more common in adult patients receiving >4 mg/day or prolonged treatment); the risk of seizures appears to be greatest 24 to 72 hours following discontinuation of therapy. Use caution when reducing dose or withdrawing therapy; decrease slowly (eg, ≤0.5 mg every 3 days in adults) and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy. Use with caution: in patients with depression, particularly if suicidal risk may be present; in patients with a history of drug abuse or acute alcoholism; in patients with hepatic impairment; in patients with porphyria; in patients with renal impairment; in patients with respiratory disease; in debilitated patients; active metabolites with extended half-lives may lead to delayed accumulation and adverse effects; in patients who are at risk of falls; in children. Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Benzodiazepines have been associated with anterograde	Alprazolam: Contraindicated in acute narrow-angle glaucoma; concurrent use with ketoconazole, itraconazole, or other potent CYP3A4 inhibitors. Chlordiazepoxide: Use with caution in patients with an impaired gag reflex. Clonazepam: Contraindicated in significant liver disease and acute narrow-angle glaucoma; Monitor all patients for notable changes in behavior that might indicate suicidal thoughts or depression; Use with caution in patients with porphyria, may have a porphyrogenic effect. Clorazepate: Contraindicated in acute narrow-angle glaucoma and Myasthenia gravis; Use with caution in the elderly, dosage adjustment recommended. Diazepam: The FDA is alerting health care providers and emergency responders that certain lots of CANA (diazepam) autoinjectors manufactured by Meridian Medical Technologies can be used beyond the labeled expiration date, which should help mitigate potential shortages of these drugs; acute narrow-angle glaucoma; Contraindicated in untreated open-angle glaucoma, infants <6 months of age (oral), myasthenia gravis, severe respiratory impairment, severe hepatic impairment, sleep apnea syndrome; When used as an adjunct in treating convulsive disorders, an increase in frequency/severity of tonic-clonic seizures may occur and require dose adjustment of anticonvulsant, abrupt withdrawal may result in a temporary increase in the frequency and/or severity of seizures; Use with caution in patients with an impaired gag reflex and in obese patients as diazepam may have prolonged action when discontinued in obese patients; Psychotic patients: Use of diazepam is not recommended in place of appropriate therapy. Lorazepam: Contraindicated in acute narrow-angle glaucoma, sleep apnea (parenteral), intra-arterial injection of parenteral formulation, severe respiratory insufficiency (except during mechanical ventilation); Psychiatric disorders: Preexisting depression may emerge or worsen during therapy, not recommended for use in primary depressive or psychotic disorders,

Warnings	Precautions	Other Considerations
	amnesia. Benzodiazepines may cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving); Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated. Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients	should not be used in patients at risk for suicide without adequate antidepressant treatment; Use with caution in patients with an impaired gag reflex; Appropriate use: as a hypnotic, should be used only after evaluation of potential causes of sleep disturbance, failure of sleep disturbance to resolve after 7 to 10 days may indicate psychiatric or medical illness, a worsening of insomnia or the emergence of new abnormalities of thought or behavior may represent unrecognized psychiatric or medical illness and requires immediate and careful evaluation. <u>Oxazepam:</u> May cause hypotension (rare), use with caution in patients with cardiovascular or cerebrovascular disease, or in patients who would not tolerate transient decreases in blood pressure; Use with caution in patients with an impaired gag reflex; Relative to other benzodiazepines, oxazepam possesses a short half-life and lacks an active metabolite which may be preferable in the elderly if benzodiazepine use is required for anxiety.

Table 8. Adverse Events Reported with the Benzodiazepine Agents*[176,177]

Adverse Effect	Alprazolam	Chlordiazepoxide	Clonazepam	Clorazepate	Diazepam	Lorazepam	Oxazepam
Cardiovascular	Hypotension (immediate-release: 5%; extended-release: <1%), chest pain (extended-release: ≥1%), palpitations (extended-release: ≥1%)	Edema, syncope	Edema (ankle or facial), palpitations	Hypotension	Hypotension, localized phlebitis, vasodilatation	Hypotension (≤2%)	Edema, hypotension, syncope
Central Nervous System	Drowsiness (immediate-release: 41% to 77%; extended-release: 23%), fatigue (immediate-release: 49%; extended-release: 14%), sedation (extended-release: 45%), ataxia (immediate-release: 40%; extended-release: 7% to 9%), memory impairment (immediate-release: 33%; extended-release: 15%), irritability (immediate-release: 33%; extended-release: ≥1%), cognitive dysfunction (immediate-release: 29%), dysarthria (immediate-release: 23%; extended-release: 11%), dizziness (immediate-release: 2% to 21%; extended-release: ≥1%), depression (extended-release: 1% to 12%); Confusion (immediate-release: 10%; extended-release: 2%), altered mental status (extended-release: 7%), disinhibition (immediate-release: 3%), disturbance in attention (extended-release: 3%), equilibrium disturbance (extended-release: 3%), akathisia (immediate-release: 2%), disorientation (extended-release: 2%), lethargy (extended-release: 2%), talkativeness (immediate-release: 2%), derealization (≥1% to 2%), agitation	Abnormal electroencephalogram, ataxia, confusion, drowsiness, drug-induced extrapyramidal reaction	Drowsiness (seizure disorder: ~50%; panic disorder: 26% to 50%), ataxia (seizure disorder: ~30%; panic disorder: 1% to 9%), behavioral problems (seizure disorder: ~25%), dizziness (panic disorder: 5% to 12%); Fatigue (panic disorder: 6% to 9%), depression (panic disorder: 6% to 8%), memory impairment (panic disorder: 4% to 5%), nervousness (panic disorder: 3% to 4%), dysarthria (panic disorder: ≤4%), reduced intellectual ability (panic disorder: ≤4%), emotional lability (panic disorder: 2%), confusion (panic disorder: ≤2%), delayed ejaculation (panic disorder ≤2%); Amnesia, aphonia, choreiform movements, coma, glassy-eyed appearance, hallucination, headache, hemiparesis, hypotonia, hysteria, insomnia, myasthenia, psychosis, slurred speech, vertigo	Anxiety, ataxia, confusion, depression, dizziness, drowsiness, dysarthria, fatigue, headache, insomnia, irritability, memory impairment, nervousness, slurred speech	Amnesia, ataxia, confusion, depression, drowsiness, dysarthria, fatigue, headache, slurred speech, vertigo	Sedation (≤16%), dizziness (≤7%), drowsiness (2% to 4%), unsteadiness (3%), headache (1%), coma (≤1%), stupor (≤1%), aggressive behavior, agitation, akathisia, amnesia, anxiety, central nervous system stimulation, disinhibition, disorientation, dysarthria, euphoria, excitement, extrapyramidal reaction, fatigue, hostility, hypothermia, irritability, mania, memory impairment, outbursts of anger, psychosis, seizures, sleep apnea (exacerbation), sleep disturbances, slurred speech, suicidal behavior, suicidal ideation, vertigo	Amnesia, ataxia, dizziness, drowsiness, drug dependence, dysarthria, euphoria, headache, lethargy, memory impairment, slurred speech, vertigo

Adverse Effect	Alprazolam	Chlordiazepoxide	Clonazepam	Clorazepate	Diazepam	Lorazepam	Oxazepam
	(extended-release: ≥1%), depersonalization (extended-release: ≥1%), headache (extended-release: ≥1%), insomnia (extended-release: ≥1%), malaise (extended-release: ≥1%), nervousness (extended-release: ≥1%), nightmares (extended-release: ≥1%), restlessness (≥1%), vertigo (extended-release: ≥1%), anxiety (extended-release: 1%), feeling hot (immediate-release: 1%; extended-release: <1%), hypersomnia (extended-release: 1%), hypoesthesia (extended-release: 1%), dystonia						
Dermatologic	Skin rash (immediate-release: 11%; extended-release: <1%); Allergic skin reaction (≤4%), dermatitis (immediate-release: ≤4%), diaphoresis (extended-release: ≥1%), pruritus (extended-release: 1%)	Skin rash	Hypersensitivity (panic disorder: 2% to 4%); Alopecia, skin rash	Skin rash	Skin rash	Alopecia, skin rash	Maculopapular rash, morbilliform rash, urticaria
Metabolic	Weight gain (immediate-release: 27%; extended-release: 5%), weight loss (immediate-release: 23%), decreased libido (6% to 14%); Menstrual disease (immediate-release: 10%; extended-release: 2%), increased libido (immediate-release: 8%; extended-release: ≥1%), change in libido (immediate-release: 7%), hot flash (extended-release: 2%)	Change in libido, menstrual disease	Decreased libido (panic disorder: ≤3%); Dehydration, hirsutism, increased libido, weight gain, weight loss	Decreased libido	Change in libido	Change in libido, hyponatremia, SIADH	Decreased libido, menstrual disease
Gastrointestinal	Increased appetite (immediate-release: 33%; extended-release: 7%), decreased appetite	Constipation, nausea	Constipation (panic disorder: 3% to 5%), decreased appetite (panic disorder: 3%), abdominal pain (panic	Constipation, decreased appetite, diarrhea,	Altered salivation (dry mouth or hypersalivation), constipation,	Changes in appetite, constipation	Nausea

Adverse Effect	Alprazolam	Chlordiazepoxide	Clonazepam	Clorazepate	Diazepam	Lorazepam	Oxazepam
	(immediate-release: 28%), constipation (immediate-release: 26%; extended-release: 8%), xerostomia (immediate-release: 15%); Nausea (extended-release: 6%), sialorrhea (immediate-release: 4% to 6%; extended-release: ≥1%), anorexia (extended-release: 2%), abdominal pain (extended-release: ≥1%), diarrhea (extended-release: ≥1%), dyspepsia (extended-release: ≥1%), vomiting (extended-release: ≥1%)		disorder: 2%); Anorexia, coated tongue, diarrhea, encopresis, gastritis, gingival pain, increased appetite, nausea, xerostomia	increased appetite, nausea, vomiting, xerostomia	diarrhea, nausea		
Hematologic	Not reported	Agranulocytosis, bone marrow depression	Anemia, eosinophilia, leukopenia, lymphadenopathy, thrombocytopenia	Not reported	Not reported	Agranulocytosis, pancytopenia, thrombocytopenia	Hematologic disease, leukopenia
Hepatic	Not reported	Hepatic insufficiency, jaundice	Hepatomegaly, increased serum alkaline phosphatase (transient), increased serum transaminases (transient)	Increased serum transaminases, jaundice	Jaundice	Increased serum alkaline phosphatase, increased serum bilirubin, increased serum transaminases, jaundice	Jaundice
Neuromuscular & skeletal	Arthralgia (extended-release: 2%), dyskinesia (extended-release: 2%), myalgia (extended-release: 2%), back pain (extended-release: ≥1%), muscle cramps (extended-release: ≥1%), muscle twitching (extended-release: ≥1%), tremor (extended-release: ≥1%), weakness (extended-release: ≥1%), limb pain (extended-release: 1%)	Not reported	Myalgia (panic disorder: 2% to 4%); Dysdiadochokinesia, tremor	Tremor	Tremor, weakness	Weakness (≤4%)	Hyporeflexia, tremor
Ophthalmic/Otic	Blurred vision (extended-release: ≥1%)	Not reported	Blurred vision (panic disorder: 2% to 3%); Abnormal eye movements, diplopia, nystagmus	Blurred vision, diplopia	Blurred vision, diplopia	Visual disturbances (including diplopia and blurred vision)	Blurred vision, diplopia
Renal	Not reported	Not reported	Dysmenorrhea (panic disorder: 3% to 6%), vaginitis (panic disorder: 2% to 4%), impotence (panic disorder:	Not reported	Urinary incontinence, urinary retention	Not reported	Urinary incontinence

Adverse Effect	Alprazolam	Chlordiazepoxide	Clonazepam	Clorazepate	Diazepam	Lorazepam	Oxazepam
			≤3%), urinary tract infection (panic disorder: ≤2%), urinary frequency (panic disorder: 1% to 2%)				
Respiratory	Dyspnea (extended-release: 2%), hyperventilation (extended-release: ≥1%), nasal congestion (extended-release: ≥1%), allergic rhinitis (extended-release: 1%)	Not reported	Upper respiratory tract infection (panic disorder: 6% to 10%), sinusitis (panic disorder: 4% to 8%), influenza (panic disorder: 4% to 5%), cough (panic disorder: ≤4%), rhinitis (panic disorder: 2% to 4%), pharyngitis (panic disorder: 2% to 3%), bronchitis (panic disorder: 2%); Chest congestion, dyspnea, respiratory depression, rhinorrhea, upper respiratory complaint (hypersecretion)	Not reported	Apnea, asthma, bradypnea	Respiratory failure (1% to 2%), apnea (1%), hypoventilation (≤1%), exacerbation of obstructive pulmonary disease, nasal congestion, respiratory depression, worsening of sleep apnea	Not reported
Miscellaneous	Difficulty in micturition (immediate-release: 12%; extended-release: ≥1%); Sexual disorder (immediate-release: 7%; extended-release: 2%), dysmenorrhea (extended-release: 4%), urinary incontinence (immediate-release: 2%; extended-release: <1%); Drug dependence, drug withdrawal; <1%, postmarketing, and/or case reports: Abnormal dreams, aggressive behavior, amnesia, angioedema, apathy, bradyphrenia, chest tightness, choking sensation, clammy skin, clumsiness, diplopia, dysgeusia, dysphagia, edema, emotional lability, epistaxis, euphoria, falling, feeling drunk, fever, galactorrhea, gastrointestinal disease, gynecomastia, hallucination, hangover effect, hepatic failure, hepatitis, homicidal ideation, hyperprolactinemia,	Paradoxical reaction	Fever, paradoxical reactions (including aggressive behavior, agitation, anxiety excitability, hostility, irritability, nervousness, nightmares, sleep disturbance, vivid dreams), physical health deterioration	Not reported	Pain at injection site; Paradoxical reaction (eg, aggressiveness, agitation, anxiety, delusions, hallucinations, inappropriate behavior, increased muscle spasms, insomnia, irritability, psychoses, rage, restlessness, sleep disturbances, stimulation)	Impotence, orgasm disturbance; Anaphylaxis, anaphylactoid reaction, hypersensitivity reaction; Pain at injection site (IM: 1% to 17%; IV: ≤2%), erythema at injection site (≤2%); <1%, postmarketing, and/or case reports: Abnormal gait, abnormal hepatic function tests, abnormality in thinking, acidosis, cardiac arrhythmia, ataxia, blood coagulation disorder, bradycardia, cardiac arrest, cardiac failure, cerebral edema, chills, confusion, convulsions, cystitis, decreased mental acuity, delirium, depression, drug dependence (with prolonged use), drug toxicity (polyethylene glycol or propylene glycol poisoning [prolonged IV infusion]), excessive crying, gastrointestinal hemorrhage, hallucinations, hearing loss,	Fixed drug eruption; Paradoxical central nervous system stimulation, paradoxical excitation

Adverse Effect	Alprazolam	Chlordiazepoxide	Clonazepam	Clorazepate	Diazepam	Lorazepam	Oxazepam
	hypomania, hypotonia, impaired consciousness, impulse control disorder, increased energy, increased liver enzymes, increased serum bilirubin, increased thirst, jaundice, jitteriness, loss of control of legs, mania, mydriasis, otalgia, outbursts of anger, peripheral edema, photophobia, psychomotor retardation, relaxation, rhinorrhea, rigors, seizure, sensation of cold, sinus tachycardia, skin photosensitivity, sleep apnea, sleep talking, Stevens-Johnson syndrome, stupor, suicidal ideation, syncope, tinnitus, urinary frequency, urticaria, voice disorder					heart block, hematologic abnormality, hepatotoxicity, hypertension, hyperventilation, hyporeflexia, infection, injection site reaction, myoclonus, nausea, nervousness, neuroleptic malignant syndrome, paralysis, pericardial effusion, pheochromocytoma (aggravation), pneumothorax, pulmonary edema, pulmonary hemorrhage, pulmonary hypertension, restlessness, seizure, sialorrhea, tachycardia, tremor, urinary incontinence, ventricular arrhythmia, vomiting, withdrawal syndrome	

Adverse events as reported in package labeling are not meant to be comparative.

Summary

The benzodiazepines are commonly used in the treatment of anxiety disorders despite lack of evidence supporting their use. Clinical guidelines do not recommend benzodiazepines as first line treatment in anxiety. According to the guidelines for treating anxiety disorders, very little evidence supports the use of benzodiazepine agents even as second line agents. If used to treat anxiety, benzodiazepines should only be used on a short-term basis (≤ 4 months). Comparative clinical evidence for the benzodiazepines in the treatment of anxiety suggests similar outcomes and rates of symptom reduction between the agents. Clinical evidence evaluating benzodiazepine use in geriatric patients and patients with a history of substance abuse is limited. It is recommended benzodiazepine use be limited in these patient populations and used only when necessary. Little comparative clinical evidence evaluating differences in adverse event rates between the agents is available. Data from included clinical trials suggest diazepam may be associated with an increased risk of sedation and lorazepam may be associated with an increased overall adverse event rate. However, differences in adverse event rates were often small and non-significant. In general, all benzodiazepines have similar adverse events but the rates of these events may differ depending on their individual pharmacokinetic profiles. Overall, benzodiazepines should be used at the lowest effective dose for the shortest time possible with a comprehensive treatment plan and careful follow-up.

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Appendix A: Evidence Tables

Evidence Table 1. Systematic Reviews Evaluating the Efficacy of Benzodiazepines in the Treatment of Anxiety Disorders

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects	Grade *
				Results	Change from baseline		
Martin et al, 2005[145] Meta-analysis of 23 experimental, double-blind, placebo-controlled, randomized controlled trials published from 1983 to 2003.	2,326	Patients aged 17-70 years with anxiety disorder. Previous anxiety treatment not reported.	Alprazolam (4 studies) Diazepam (12 studies) Lorazepam (7 studies) Placebo (23 studies) n for each treatment group was not reported Duration of treatment: 2 – 24 weeks.	Alprazolam = Diazepam = Lorazepam ≥ Placebo	Relative Risk for Withdrawals for any reason: • Alprazolam: 0.58 • Diazepam: 0.80 • Lorazepam: 1.12	Not Reported	1

Evidence Table 2. Clinical Trials Evaluating the Efficacy of Benzodiazepines in the Treatment of Anxiety Disorders

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects	Grade *
				Results	Change from baseline		
Cohn et al, 1984[146] Experimental, parallel, double-blind, randomized	200	Adult patients aged 18-62 with moderate to severe anxiety. Previous anxiety treatment not reported.	Alprazolam 1-4.5mg/day; mean 3.3mg/day (n = 80) Lorazepam 2-9mg/day; mean 5.1mg/day (n = 80) Placebo (n = 40) Duration: Seven day wash-out period followed by 16 weeks of treatment.	Alprazolam = Lorazepam > Placebo	<u>Improvement in Hamilton Anxiety Rating Score:</u> Alprazolam = Lorazepam > Placebo, $p < 0.05$ (p = NS between treatment groups)	<u>Discontinuation due to adverse event:</u> • Alprazolam: 9 (11.3%) • Lorazepam: 16 (20%) • Placebo: 6 (15%) <u>Discontinuation due to lack of efficacy:</u> • Alprazolam: 1 (1.3%) • Lorazepam: 6 (7.5%) • Placebo: 18 (45%)	1

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects	Grade *
				Results	Change from baseline		
Schweizer et al, 1988[153] Experimental, multicenter, parallel, double-blind, randomized	38	Adult patients with panic disorder. <u>Previous anxiety treatment</u> Benzodiazepine: -Alprazolam group: 6/19 patients -Lorazepam group: 12/19 patients Other Medication: -Alprazolam group: 2/19 patients -Lorazepam group: 1/19 patients	Alprazolam 0.5-8mg/day (n = 19) Lorazepam 1-16mg/day (n = 19) Mean daily doses not reported. Duration: Seven day wash-out period followed by 6 weeks of treatment.	Alprazolam = Lorazepam	<u>Hamilton Anxiety Rating Score:</u> Baseline • Alprazolam: 22.2 • Lorazepam: 22.6 Week 6 • Alprazolam: 10.2 • Lorazepam: 11.3 (p = NS between treatment groups)	<u>Discontinuation due to adverse event:</u> • Alprazolam: 0 (0%) • Lorazepam: 4 (21%) <u>Discontinuation due to lack of efficacy:</u> • Alprazolam: 1 (5%) • Lorazepam: 0 (0%)	1

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects	Grade *
				Results	Change from baseline		
Schweizer et al, 1990[154] Experimental, multicenter, parallel, double-blind, randomized	60	Adult patients with panic disorder. Previous anxiety treatment with a benzodiazepine reported in 11 patients (16%).	Alprazolam 0.5-8mg/day; mean dose 3mg/day (n = 30) Lorazepam 1-16mg/day; mean dose 7mg/day (n = 30) Duration: Seven day wash-out period followed by 6 weeks of treatment.	Alprazolam = Lorazepam	<u>Hamilton Anxiety Rating Score:</u> Baseline • Alprazolam: 18.3 ± 9 • Lorazepam: 19.4 ± 8 Week 6 • Alprazolam: 8.9 ± 8 • Lorazepam: 11.3 ± 10 <u>General Hopkins Symptom Score:</u> Baseline • Alprazolam: 9.1 ± 9 • Lorazepam: 10.4 ± 7 Week 6 • Alprazolam: 4.6 ± 6 • Lorazepam: 5.1 ± 7 <u>Number of Panic Attacks:</u> Baseline • Alprazolam: 5.1 ± 7.6 • Lorazepam: 7.0 ± 7.1 Week 6 • Alprazolam: 1.8 ± 2.4 • Lorazepam: 2.6 ± 3.7 <u>Degree of Phobic Avoidance:</u> Baseline • Alprazolam: 5 ± 2.5 • Lorazepam: 5.9 ± 2 Week 6 • Alprazolam: 2.7 ± 2.5 • Lorazepam: 3.4 ± 2.6 (p = NS between treatment groups)	<u>Adverse event rate:</u> Mild • Alprazolam: 7 (21%) • Lorazepam: 11 (33%) Moderate • Alprazolam: 16 (47%) • Lorazepam: 15 (45%) Severe • Alprazolam: 7 (21%) • Lorazepam: 6 (18%) <u>Sedation:</u> • Alprazolam: 74% • Lorazepam: 76% <u>Vertigo:</u> • Alprazolam: 6% • Lorazepam: 15% <u>Nausea:</u> • Alprazolam: 6% • Lorazepam: 18% <u>Asthenia:</u> • Alprazolam: 9% • Lorazepam: 12%	1

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects	Grade *
				Results	Change from baseline		
Elie et al, 1984[147] Experimental, parallel, double-blind, randomized	48	Adults with mild to moderate generalized anxiety. Prior treatment with oxazepam (n = 24), lorazepam (n = 13), or no prior treatment (n = 11).	Alprazolam 0.5-3 mg/day (n = 24) Diazepam 5-25 mg/day (n = 24) Duration: 5-day wash-out period followed by 30 days of active treatment.	Diazepam > Alprazolam	<u>Total Hamilton Anxiety Rating Score:</u> Baseline • Alprazolam: 26.64 • Diazepam: 24.92 Week 4 • Alprazolam: 9.82 • Diazepam: 7.21 <u>Hamilton Anxiety Rating Depressed Mood Score:</u> Week 2 • Alprazolam: 0.83 • Diazepam: 0.45, $p < 0.05$ Week 4 • Alprazolam: 0.73 • Diazepam: 0.33, $p < 0.05$ <u>Global Behavior Score:</u> Baseline • Alprazolam: 12.23 • Diazepam: 10.96 Week 4 • Alprazolam: 3.36 • Diazepam: 2.3 <u>General Hopkins Symptom Score:</u> Baseline • Alprazolam: 26.91 • Diazepam: 22.16 Week 4 • Alprazolam: 17.27 • Diazepam: 13.04 (p = NS between groups unless noted)	<u>Drowsiness:</u> • Alprazolam: 7 (29%) • Diazepam: 5 (21%) <u>Tremor:</u> • Alprazolam: 4 (17%) • Diazepam: 7 (29%) <u>Light-headedness:</u> • Alprazolam: 5 (21%) • Diazepam: 3 (13%) <u>Dry mouth:</u> • Alprazolam: 4 (17%) • Diazepam: 2 (8%)	1

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects	Grade *
				Results	Change from baseline		
Rickels et al, 1983[150] Experimental, parallel, double-blind, randomized	151	Adults with moderate to severe anxiety symptoms for > 4 weeks. Previous anxiety treatment not reported.	Alprazolam 0.6-2.7 mg/day (n = 54) Diazepam 10-45 mg/day (n= 45) Placebo (n = 52) Duration: 7-day wash-out period followed by 4 weeks of treatment.	Alprazolam = Diazepam > Placebo	<u>Total Hamilton Anxiety Score:</u> Baseline: 24.22 Week 4: • Alprazolam: 9.52 • Diazepam: 11.2 • Placebo: 16.66 <u>Hopkins Anxiety Score:</u> Baseline: 2.17 Week 4: • Alprazolam: 1.49 • Diazepam: 1.53 • Placebo: 1.78 <u>Global Improvement:</u> • Alprazolam: 2.39 • Diazepam: 2.64 • Placebo: 3.39 (p = NS between treatment groups)	<u>Discontinuation Rate:</u> • Alprazolam: 1 • Diazepam: 6 • Placebo: 2 <u>Sedation:</u> Week1: • Alprazolam: 28 (53%) • Diazepam: 29 (64%) • Placebo: 18 (38%) Week 2: • Alprazolam: 26 (48%) • Diazepam: 32 (74%), $p < 0.05$ • Placebo: 18 (39%)	1

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects	Grade *
				Results	Change from baseline		
Vaisanen et al, 1987[155] Experimental, parallel, double-blind, randomized	60	Patients aged 18-60 years with moderate to severe anxiety ≥ 1 month. Previous anxiety treatment not reported.	Alprazolam 0.5-3mg/day (n = 30) Oxazepam 15-90mg/day (n = 30) Duration: 4-7 day placebo wash-out period followed by 4-weeks of active treatment.	Alprazolam = Oxazepam	Change in Lipman Self-Rating Score: • Alprazolam: -3.0 • Oxazepam: -1.9 Change in Hamilton Anxiety Rating Score: • Alprazolam: -14.28 • Oxazepam: -11.9 (p = NS between treatment groups)	Discontinuation Rate: • Alprazolam: 1 • Oxazepam: 5 Insomnia: • Alprazolam: 8 • Oxazepam: 3 Drowsiness: • Alprazolam: 6 • Oxazepam: 6 Depression: • Alprazolam: 6 • Oxazepam: 5 Tachycardia/palpitations: • Alprazolam: 5 • Oxazepam: 4 Dry mouth: • Alprazolam: 5 • Oxazepam: 0 Blurred vision/lightheadedness: • Alprazolam: 3 • Oxazepam: 7 GI disturbances: • Alprazolam: 2 • Oxazepam: 7 Headache: • Alprazolam: 5 • Oxazepam: 4	1

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects	Grade *
				Results	Change from baseline		
Rimon et al, 1991[152] Experimental, multicenter, parallel, double-blind, randomized	62	Adult patients with an anxiety disorder. Seventeen patients received previous anxiety treatment.	Alprazolam 0.25mg three times daily (n = 32) Oxazepam 7.5mg three times daily (n = 30) Dose adjustment was allowed. Average daily dose for alprazolam = 1.48 mg and average daily dose for oxazepam = 44.4 mg. Duration: Four day wash-out period followed by 4 weeks of treatment.	Alprazolam = Oxazepam	<u>Hamilton Anxiety Rating Score:</u> Baseline • Alprazolam: 25.1 ± 6.9 • Oxazepam: 26.3 ± 5.8 Week 4 • Alprazolam: 12.1 ± 15.9 • Oxazepam: 14.6 ± 5.3 <u>Rimon's Brief Depression Scale Score (21-point scale):</u> Baseline • Alprazolam: 9.1 ± 3.7 • Oxazepam: 10 ± 3.9 Week 4 • Alprazolam: 3.8 ± 3.6 • Oxazepam: 5.6 ± 3.8 <u>Objective Global Impression Score (5-point scale):</u> Baseline • Alprazolam: 2.9 ± 0.7 • Oxazepam: 3.0 ± 0.6 Week 4 • Alprazolam: 1.9 ± 0.6 • Oxazepam: 2.1 ± 0.6 <u>Subjective Global Impression Score (5-point scale):</u> Baseline • Alprazolam: 3.2 ± 0.7 • Oxazepam: 3.3 ± 0.6 Week 4 • Alprazolam: 1.9 ± 0.6 • Oxazepam: 2.3 ± 0.6 (p = NS between treatment groups)	<u>Discontinuation Rate:</u> • Alprazolam: 2 (6%) • Oxazepam: 2 (7%) <u>Adverse Event Rate:</u> • Alprazolam: 13 (41%) • Oxazepam: 15 (50%)	1

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects	Grade *
				Results	Change from baseline		
Lydiard et al, 1991[149] Experimental, multicenter, parallel, double-blind, randomized	94	Patients aged 18-65 years with panic disorder. Previous anxiety treatment not reported.	Alprazolam 2mg/day (n = 30) Alprazolam 6mg/day (n = 31) Placebo (n = 33) Duration: One-week drug free period followed by 6-weeks of treatment.	Alprazolam 2mg = Alprazolam 6mg > Placebo	<u>Weekly Panic Attack Frequency:</u> Baseline • Alprazolam 2mg: 5.29 • Alprazolam 6mg: 6.60 • Placebo: 7.46 Week 6 • Alprazolam 2mg: 1.04 • Alprazolam 6mg: 1.00 • Placebo: 3.73 (p = NS between treatment groups)	<u>Drop-out rate due to adverse events:</u> • Alprazolam 2mg: 0 (0%) • Alprazolam 6mg: 12 (38%) • Placebo: 1 (3%) <u>Impaired coordination:</u> • Alprazolam 2mg: 40% • Alprazolam 6mg: 61.3% <u>Slurred speech:</u> • Alprazolam 2mg: 33.3% • Alprazolam 6mg: 61.3% <u>Sedation/drowsiness:</u> • Alprazolam 2mg: 83.3% • Alprazolam 6mg: 83.9% <u>Tachycardia/palpitations:</u> • Alprazolam 2mg: 17% • Alprazolam 6mg: 6% • Placebo: 27%	1

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects	Grade *
				Results	Change from baseline		
Lapierre et al, 1975[148] Experimental, parallel, double-blind, randomized	30	Outpatients aged 18–54 with a primary symptom of anxiety. Previous anxiety treatment not reported.	Chlorazepate 7.5mg/day Diazepam 5mg/day Placebo n for each treatment group was not reported Duration: Seven day wash-out period followed by 4 weeks of treatment.	Chlorazepate = Diazepam ≥ Placebo	<u>Improvement in Hamilton Anxiety Rating Score:</u> Diazepam ≥ Chlorazepate = Placebo <u>Improvement in Wittenborn Psychiatric Rating Score:</u> Diazepam ≥ Chlorazepate ≥ Placebo <u>Improvement in Global Impression Score (5-point scale):</u> Diazepam = Placebo > Chlorazepate (p = NS between treatment groups)	Not Reported	1
Rickels et al, 1988[151] Experimental, parallel, double-blind, randomized	62	Adults with generalized anxiety disorder. Previous anxiety treatment not reported.	Clorazepate 15-30 mg/day (n = 32) Lorazepam 2-4 mg/day (n= 30) Placebo (n = 52) Duration: One week wash-out period followed by 4 weeks of active treatment and an additional 2-week post-treatment period.	Clorazepate = Lorazepam > Placebo	<u>Hamilton Anxiety Score:</u> Baseline: 27.3 Week 4: • Clorazepate: 9.5 • Lorazepam: 8.6 <u>POMS Tension-Anxiety Score:</u> Baseline: 22.5 Week 4: • Clorazepate: 13.7 • Lorazepam: 12.5 <u>Global Improvement:</u> • Clorazepate: 3.1 • Lorazepam: 3.1 (p = NS between treatment groups)	<u>Discontinuation Rate:</u> • Clorazepate: 1 • Lorazepam: 3 <u>Adverse Event Rate:</u> Week 1 • Clorazepate: 15.6 • Lorazepam: 43.3, p<0.05 Week 2 • Clorazepate: 25.8 • Lorazepam: 25 Week 3 • Clorazepate: 22.6 • Lorazepam: 21.4 Week 4 • Clorazepate: 19.4 • Lorazepam: 3.7	1

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects	Grade *
				Results	Change from baseline		
Tesar et al, 1991[178] Experimental, parallel, double-blind, randomized	72	Adult patients with panic disorder. Previous anxiety treatment not reported.	Alprazolam Clonazepam Placebo Duration: 6-weeks	Alprazolam = Clonazepam > Placebo	<u>Frequency of panic attacks:</u> Alprazolam = Clonazepam > Placebo <u>Overall phobia ratings:</u> Alprazolam = Clonazepam > Placebo <u>Extent of disability:</u> Alprazolam = Clonazepam > Placebo (p = NS between treatment groups)	Comparative Data Not Reported.	1
Cohn et al, 1981[179] Experimental, multi-center, parallel, double-blind, randomized	976	Outpatient adults with anxiety syndrome. Previous anxiety treatment not reported.	Alprazolam (n = 326) Diazepam (n = 344) Placebo (n = 306) Duration: 4-weeks	Alprazolam > Diazepam > Placebo	<u>Hamilton Anxiety Rating Scale:</u> Alprazolam > Diazepam > Placebo, p > 0.05 <u>Physician's Global Assessment:</u> Alprazolam > Diazepam > Placebo, p > 0.05 <u>Patient's Global Assessment:</u> Alprazolam > Diazepam > Placebo, p > 0.05 <u>Target Symptoms</u> Alprazolam > Diazepam > Placebo, p > 0.05	Not reported.	1

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects	Grade *
				Results	Change from baseline		
Ruiz et al, 1983[180] Experimental, parallel, double-blind, randomized	53	Psychoneurotic adult outpatients. Previous anxiety treatment not reported.	Alprazolam Lorazepam Duration: 4-weeks	Alprazolam ≥ Lorazepam	<u>Autonomic symptoms:</u> Week 1: Alprazolam > Lorazepam <u>Dizziness:</u> Week 4: Alprazolam > Lorazepam All other symptom perameters were NS between treatment groups.	Comparative Data Not Reported.	1

Abbreviations: CI = confidence interval; IOP = intraocular pressure; N or n = number of patients in trial or treatment groups; NS = non-significant
*Grade = Grades of Scientific Evidence; Grade 1: Evidence from randomized, blinded, placebo-controlled, clinical trials in peer reviewed journals