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REVIEW

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Benzodiazepines at the crossroads: navigating therapeutic promise and perils of misuse

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Abstract

Benzodiazepines (BZDs) are a widely prescribed class of psychoactive drugs known for their rapid anxiolytic, anticonvulsant, and sedative effects. Introduced as safer alternatives to barbiturates, BZDs quickly gained popularity across clinical settings but have since become a subject of public health concern due to rising rates of misuse, dependence, and overdose, particularly when co-administered with opioids. This narrative review explores the historical development, pharmacologic mechanisms, clinical indications, and adverse outcomes associated with BZD use, while highlighting emerging areas of research such as pharmacogenetics (PGx) and genome-wide association studies (GWAS). BZDs act as positive allosteric modulators of the $GABA_A$ receptor, enhancing inhibitory neurotransmission. This mechanism underlies both their therapeutic efficacy and their potential for physiological dependence and misuse. Clinical applications span acute anxiety, insomnia, seizure management, and alcohol withdrawal; however, long-term use carries significant risks including cognitive decline, fall-related injuries, paradoxical excitation, and withdrawal syndromes. Reinforcement and neuroadaptation processes within the mesolimbic dopamine system contribute to BZD addiction, especially with chronic exposure. Regulatory responses include Schedule IV classification under the Controlled Substances Act and FDA black box warnings. Despite declining prescription rates in recent years, misuse, including nonmedical use and use of illicit designer BZDs, remains prevalent, especially among older adults and those with comorbid psychiatric or substance use disorders. Pharmacogenomic studies have identified genetic polymorphisms in hepatic enzymes (e.g., *Cyp2c19* and *Cyp3a4*) and $GABA_A$ receptor subunits (e.g. *Gabra2*) that may influence BZD metabolism, efficacy, and addiction vulnerability, suggesting potential for personalized medicine approaches. In conclusion, the dual nature of BZDs, as essential tools in acute care and potential contributors to substance use disorders, demands a balanced, evidence-informed approach. Continued research, improved prescriber education, and integration of genetic insights into clinical care may help mitigate harm while preserving therapeutic benefit.

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Introduction: clinical promise and public health use

The impact of pharmaceutical agents often embodies a therapeutic duality, offering substantial clinical benefit while also carrying the potential for harm. Thalidomide and opioid analgesics illustrate this principle: both introduced as medical breakthroughs, each later revealed profound risks when misused or prescribed beyond their therapeutic scope [1–6]. Such examples underscore that pharmacologic interventions exist along a continuum from healing to harm, where efficacy and toxicity frequently coexist. Similarly, benzodiazepines (BZDs) epitomize this balance. Initially developed as safer alternatives to barbiturates, they remain among the most prescribed psychotropic medications worldwide due to their rapid and reliable anxiolytic, sedative, and anticonvulsant effects [7, 8]. Yet their therapeutic success has been paralleled by rising concerns regarding overuse, dependence, and overdose, particularly when co-administered with opioids [9–11]. Historical and contemporary data illustrating changes in BZD prescribing, overdose mortality, and nonmedical use are summarized in Table 1, which highlights an early period of rapid adoption followed by increasing regulatory oversight as evidence of misuse accumulated [9,10,12-19].

Understanding these competing clinical and societal forces is essential for informed prescribing and public health policy. To maximize therapeutic benefit while minimizing harm, this narrative review examines the trajectory of BZD use from discovery to modern regulation, integrating clinical, neurobiological, and genetic perspectives to contextualize their enduring promise and ongoing challenges.

Methods of review

This narrative review synthesized current evidence on the history, biochemistry, clinical use, and contemporary literature on benzodiazepines. Relevant literature was identified through a comprehensive search of the PubMed database covering articles from the 20th century through the present day. An inclusive date range was utilized to capture the historical origins of this drug class, which came into practice in the 20th century. Various key terms were used for this search including "benzodiazepines", "benzodiazepines substance use disorder", "benzodiazepines neurobiology of addiction", "benzodiazepines prescribing patterns", "benzodiazepines pharmacogenomics", "benzodiazepines genetic variants" and "benzodiazepines clinical indication". Studies were included if they were published in English, focused on the relevant sub-topics present in the article, and provided empirical evidence related to our article's objective. Editorials and commentaries were avoided, with our goal to prioritize original research articles. Reviews were utilized when necessary to identify more extensive information as needed. The selection and integration of these articles were guided by their thematic relevance rather than through systematic criteria, allowing for an exhaustive discussion of emerging themes and perspectives in the field. However, because this review did not follow systematic methodology, potential selection bias cannot be fully excluded. The findings should therefore be interpreted as an integrative,

Table 1 Historical data demonstrating the evolution of BZD prescribing, overdose mortality, and nonmedical use

Domain	Metric/key finding	Geography	Timeframe	Key figure (s)	Source
Historical prescribing	BZD prescriptions increased from 32 M → 45 M	UK	1961–1973	+13 M scripts	[12]
Historical prescribing	Diazepam was the most prescribed U.S. drug; 2.3B doses sold in 1978	U.S.	1969–1982 (peak 1978)	2.3B doses (1978)	[13]
Nonmedical use/ED Burden	6.5 M Americans using BZDs non-medically; 7/Top-50 ED-implicated drugs were BZDs (over half suicide attempts)	U.S.	1985	6.5 M; 7/50	[12, 14]
Prescribing volume	Adults filling BZD prescriptions increased 67%	U.S.	1996–2013	+67%	[10]
Mortality	BZD overdose mortality rose 0.9 → 4.4 per 100,000	U.S.	1999–2016	~5× increase	[10]
Primary care utilization	Primary-care BZD visits nearly doubled	U.S.	2003–2015	~2×	[9]
Polypharmacy risk	>10× higher opioid-related death risk with BZD co-administration	U.S.	1999–2017	>10×	[15]
Population use & misuse	10% of people used a BZD (as-prescribed or not); 1.4% misused (≈14% of users misused)	U.S.	2022	10% use; 1.4% misuse	[16]
Designer BZDs/poisonings	Marked rise in designer BZD poisonings (e.g., clonazolam, flualprazolam)	Netherlands	2010–2020	Significant increase	[17]
Designer BZDs/case severity	Clonazolam intoxication case report (severity and risk)	U.S.	2022	Case	[18]
Global consumption	Sales-based analysis of BZDs & Z-drugs across 67 countries shows heterogeneous trends	Global (67 countries)	2008–2018	Mixed trends	[19]
Recent U.S. prescribing trend	Decline in BZD prescribing across age groups (does not capture illicit use)	U.S.	Since ~2016	Downward trend	[19]

narrative synthesis rather than a comprehensive systematic evaluation of all available evidence.

Origins: development and early adoption of BZDs

BZDs were historically preceded by barbiturates, which were first prepared in 1864 by J.F.W. Adolph von Baeyer in the form of barbituric acid, so named by the combination of "Barbara" and "urea" [20]. Barbiturates became the predominant sedative and hypnotic agents in clinical practice, but this discovery motivated a series of investigations to synthesize more compounds with sedative, hypnotic, and anesthetic effects. The cumulative synthetic chemistry efforts in 1946 led to the synthesis of mephenesin, the first tranquilizer, and soon after meprobamate, which was to become the first commercially successful and widely used non-barbiturate sedative hypnotic [21, 22]. Meprobamate was so successful that it was to be found in bathroom cabinets across the U.S. and known as "mother's little helper" [22]. Soon after, in 1955, Dr. Leo Henryk Sternbach discovered the first BZD, chlordiazepoxide and Hoffmann-La Roche bought the product [23]. The transformation of a quinazoline-3 oxide into a benzodiazepine 4-oxide resulted in a pronounced taming effect on monkeys, later prompting interest in the synthesis of related products and a subsequent patent application [24]. Interestingly, Sternbach's initial chemical synthesis of 40 new compounds did not produce the expected repertoire of sedative, anticonvulsant, or relaxant properties. These results were disappointing, but over a year later, a colleague of Sternbach, Earl Reeder, raised interest in two crystallized products left over from Sternbach's initial studies of the analogues. These products were evaluated in trials and demonstrated to be superior to meprobamate in terms of anxiolytic and relaxant activity, some sedative properties, and lacked significant safety concerns [25]. After intense analysis of the pharmacologic activity of the benzodiazepine 4-oxide analogues, none were superior to the methylamino derivative named, "13" [24]. The notable anxiolytic effects paired with low toxicity prompted full marketing of this compound named 7-chloro-2-(methylamino)–5-phenyl-3*H*–1,4-benzodiazepine 4-oxide in 1960 under the trademark, Librium [24, 26].

Continued research into compounds with higher potency eventually led to the identification of diazepam, which is 3 to 10 times as potent as chlordiazepoxide [24, 27]. Clinical trials were initiated in the 1960s to evaluate the clinical safety and efficacy of oxazepam, a short-to-intermediate-acting benzodiazepine [27, 28]. Pharmaceutical development has produced countless other benzodiazepines for clinical use such as clorazepate, lorazepam, alprazolam, and clonazepam (see section on *Clinical indications, efficacy, and risks*) [27]. Clinical efficacy of alprazolam was evaluated later in the 1970s and 1980s in patients diagnosed with anxiety and depression. Comparative studies evaluating alprazolam to diazepam demonstrate similar efficacy, with reports supporting superior efficacy of alprazolam to diazepam in terms of anxiolytic effects. Drowsiness, a common side effect seen in patients prescribed benzodiazepines, was shown to be significantly less in patients receiving alprazolam compared to diazepam [29–31]. Ultimately, due to their improved therapeutic index resulting in decreased risk of overdose, BZDs overtook barbiturates in popularity. These foundational discoveries set the stage for understanding BZDs' mechanism of actionand clinical expansion.

Mechanisms of action: GABAergic modulation and receptor targets

BZDs are a class of drugs that allosterically modulate gamma-aminobutyric acid $(GABA)_A$ receptors, a heteromeric ligand-gated ion channel, by binding to the BZD binding site potentiating the effects of GABA. GABA is the primary inhibitory neurotransmitter in the central nervous system (CNS), and this accounts for the profound hypnotic and anxiolytic effects that distinguish BZDs [32, 33] (Fig 1). In contrast to the mechanism of action of barbiturates, which is to increase the *duration* of $GABA_A$ receptor opening, BZDs increase the *frequency* of $GABA_A$ receptor opening, with eventual plateauing of its effect [34]. Through their activity on $GABA_A$ receptors, BZDs are effective medications for treating episodic anxiety, acute stress reactions, management of seizures, certain cases of insomnia, severe panic disorder, and alcohol withdrawal management, with a relatively more favorable side effect profile compared to other psychotropic drugs [35].

The $GABA_A$ is a heteropentameric complex typically composed of two α, two β, and one γ subunit, with six α subtypes (α1–6) conferring distinct functional properties. Among these, α1, 2, 3, and 5 subunits are most relevant to the pharmacology of clinically used BZDs. Subtype-selective actions explain the differential therapeutic and adverse effects observed across agents:

- α1-containing receptors mediate sedation, anterograde amnesia, and anticonvulsant effects.
- α2 and α3 subunits are primarily responsible for anxiolysis and myorelaxation.
- α5 subunits, enriched in hippocampal regions, are associated with cognitive slowing and memory impairment [36–38].

Clinically, these subtype distinctions matter because most traditional BZDs, including diazepam, clonazepam, and alprazolam, act non-selectively across α subtypes. While this broad binding profile produces potent

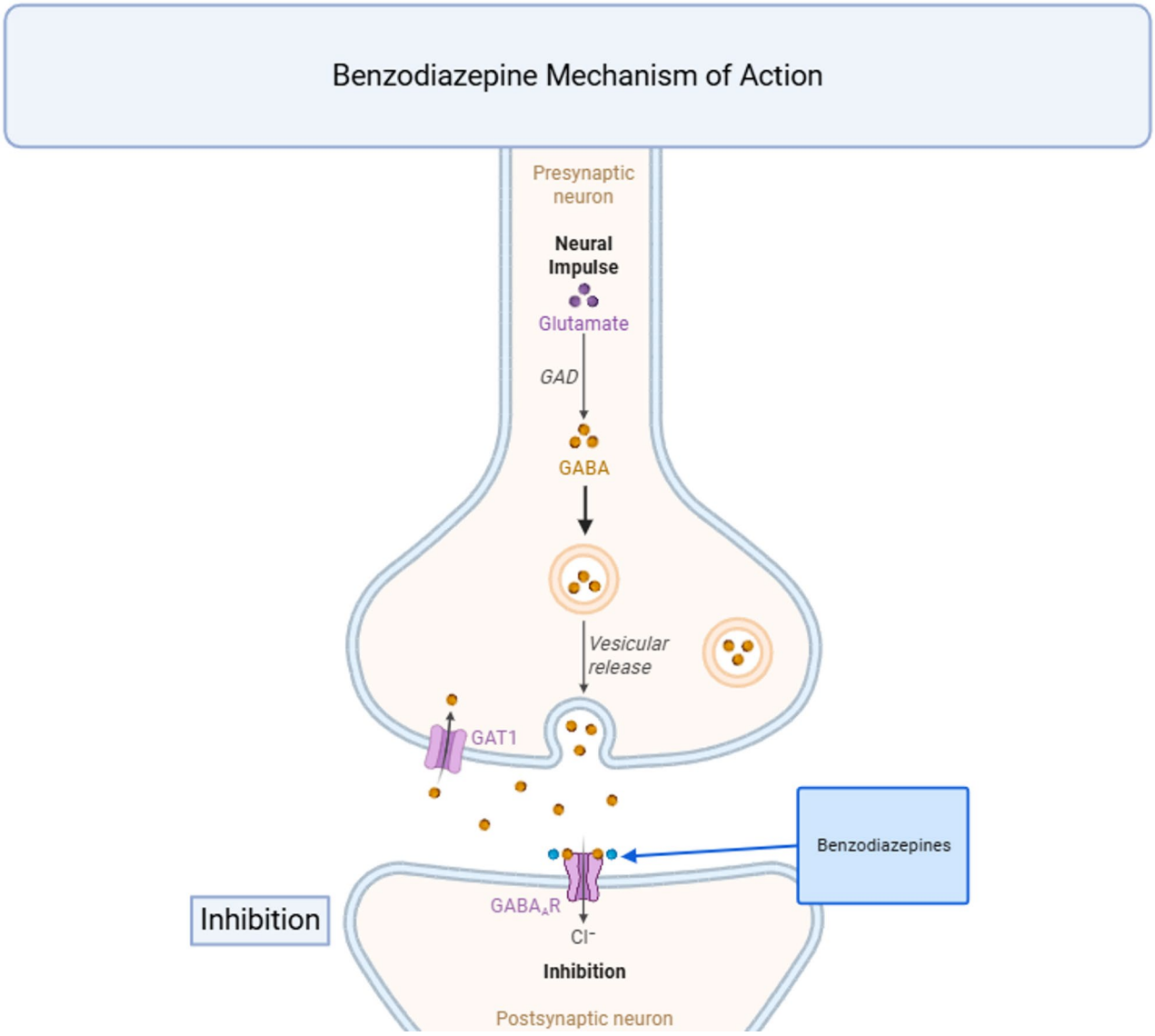

Fig. 1 The mechanism of action for BZD relies on modulation of the $GABA_A$ receptor. Benzodiazepines enhance inhibitory neurotransmission by binding allosterically to $GABA_A$ receptors at the postsynaptic membrane. Upon neural impulse arrival, glutamate activates GAD (glutamic acid decarboxylase), which converts glutamate to GABA. GABA is then released into the synaptic cleft, where it binds to $GABA_A$ receptors, facilitating chloride (Cl^-) influx and hyperpolarization of the postsynaptic neuron. Benzodiazepines increase the frequency of $GABA_A$ receptor channel opening, amplifying this inhibitory effect. GABA reuptake is mediated by GABA Transporter Type 1 (GAT1) on the presynaptic neuron

symptomatic relief, it also contributes to unwanted effects such as sedation, dependence, and cognitive dysfunction. Consequently, receptor selectivity has become a central focus of next-generation drug design. Novel "subtype-selective" compounds, such as L-838,417 and TPA023, preferentially modulate α2 and α3 containing receptors, preserving anxiolytic efficacy while reducing α1 and α5-related adverse effects like drowsiness and amnesia [36, 39].

This receptor-level specificity offers a translational pathway toward safer anxiolytic pharmacotherapies that maintain efficacy while lowering misuse liability. By decoupling anxiolysis from sedation and reinforcing pathways, subtype-selective and partial agonists may overcome the limitations of classical BZDs. Integration of these pharmacologic innovations with pharmacogenetic insights into subunit expression variability could further refine treatment strategies, enabling personalized modulation of GABAergic signaling for anxiety and sleep disorders. This pharmacological understanding provides the foundation for their diverse clinical applications and helps explain both efficacy and side effects.

Clinical indications, efficacy, and risks

BZDs provide rapid anxiolytic effects, making them particularly useful for the short-term management of acute

Table 2 Common benzodiazepines have various indications and side effects. Certain modalities can impact the modulation of effects and side effects in each drug. Acute anxiety is the primary indication for most BZDs

Name	Trade name	Duration of action	Modality	Primary effects	Notable side effects	Common indications
Diazepam	Valium, Valtoco	Long-acting	Oral, intravaginal, IV, IM, rectal, nasal	Anxiolytic, antiepileptic, anticonvulsant, muscle relaxant	Drowsiness, confusion, dizziness, respiratory depression	Anxiety, epilepsy, febrile seizures, muscle spasms, alcohol withdrawal, insomnia, restless syndrome, pre/post-operative sedation
Alprazolam	Xanax, Niravam	Short-acting	Oral	Anxiolytic, antidepressant	Drowsiness, confusion, memory impairment, potential for dependence	Anxiety disorder, panic disorder, schizophrenia, cancer, premenstrual syndrome,
Midazolam	Versed, Nayzilam	Short-acting	IV, IM, oral, nasal, rectal	Sedative, anxiolytic, amnesic	Respiratory depression, hypotension, amnesia, cough, nausea, vomiting	Procedural sedation, induction of anesthesia, status epilepticus
Lorazepam	Ativan	Short-acting	Oral, IV	Anxiolytic, anticonvulsant, sedative	Drowsiness, dizziness, fatigue, potential for dependence	Anxiety disorders, insomnia, preoperative sedation, status epilepticus
Clonazepam	Klonopin	Long	Oral	Anxiolytic, anticonvulsant	Drowsiness, motor impairment, potential for dependence	Panic disorder, seizure disorders, acute mania

situational anxiety [40, 41]. They can be administered via multiple routes, including intramuscular, intravenous, oral, sublingual, intranasal, and rectal gel. Anxiolysis typically begins within 30 to 60 min following oral or parenteral administration [42]. Other indications and routes of administration for various BZDs are included in Table 2 [23, 27, 28, 33] (Table 2).

BZDs are employed for a wide range of clinical indications, including insomnia, depression (with or without anxiety), catatonia, functional gastrointestinal complaints, coronary heart disease, alcohol withdrawal, and agitation [43–46]. In the context of insomnia, BZDs have demonstrated short-term efficacy by reducing sleep onset latency and increasing total sleep duration [47]. They are FDA-approved for anxiety, alcohol withdrawal, seizures, preoperative and procedural sedation, and panic disorder, among other uses [33]. Alprazolam, for example, has shown superior efficacy over placebo in treating panic disorder and demonstrated comparable effectiveness to other pharmacologic comparators [42]. A meta-analysis of treatments for social anxiety disorder also found BZDs to be more effective than antidepressants and anticonvulsants, with a significantly lower relapse rate [48].

Off-label, BZDs are sometimes prescribed as adjuncts to antipsychotic therapy for managing agitation or hostility in patients with schizophrenia, though clinical trial results have been inconsistent [49, 50]. Studies comparing BZD-antipsychotic combinations to antipsychotics alone show variable outcomes, with interpretations limited by short durations, diverse methodologies, high attrition rates, and incomplete reporting [50].

BZDs are first-line agents for managing seizure clusters due to their rapid onset of action. While rectal diazepam was the first FDA-approved formulation, newer intranasal preparations (midazolam and diazepam) allow for more practical and socially acceptable administration. Despite their clinical utility, BZD rescue therapies remain underutilized, in part due to lack of familiarity among patients and caregivers [51]. Successful implementation requires structured seizure action plans and appropriate staff training to ensure timely and effective use [52].

In the treatment of comorbid mood disorders, the use of BZDs is generally discouraged due to their risk of dependence, behavioral disinhibition, and potential to exacerbate suicidal ideation. Nonetheless, they continue to be widely prescribed— often influenced by co-occurring anxiety disorders, patient preferences, and symptom-driven prescribing approaches [53]. Importantly, BZDs are contraindicated in patients with post-traumatic stress disorder (PTSD), as evidence suggests they may interfere with extinction learning, impair recovery, and worsen overall outcomes [33].

Use of BZDs during pregnancy requires caution. Evidence suggests potential associations with spontaneous abortion, preterm birth, and reduced birth weight, though most studies have not demonstrated a significant increase in congenital malformations. Combined BZD and antidepressant exposure during pregnancy has not been linked to increased congenital risks in large cohort analyses, including data from Taiwan [54, 55].

Common adverse effects of BZDs include physical dependence, withdrawal symptoms, increased fall risk, memory impairment, daytime sedation, functional decline, and higher rates of motor vehicle accidents. These risks are amplified by concurrent alcohol use and increase with patient age. For example, among patients prescribed long-acting BZDs, those aged 80 to 84 demonstrated the highest fall risk, particularly with longer durations of use [47].

Although rare, paradoxical or atypical reactions occur in less than 1% of BZD users [14]. Known as "paradoxical

excitation," these responses may involve agitation, restlessness, aggression, or sexual disinhibition [56]. Despite long-standing clinical recognition, the underlying pathophysiology remains unclear. Recent zebrafish models have implicated serotonin-6 receptor (HTR6) antagonism in paradoxical excitation following $GABA_A$ receptor modulation, though these findings are limited by species differences, single-drug evaluation (diazepam), and receptor subunit diversity in humans [56, 57]. However, the field remains constrained by few models of paradoxical excitation. Importantly, paradoxical excitation from BZDs has been documented across multiple species including dogs, which offers the potential of a large animal model for understanding BZD biology [58–60]. Risk factors for paradoxical reactions include extremes of age, high doses or rapid infusion rates, alcohol use disorder, and comorbid psychiatric illness [61, 62]. A rare case involving twins suggests a possible genetic predisposition, but further research is needed to confirm any heritable contribution to this phenomenon [63].

Like most pharmacologic agents, BZDs carry both therapeutic benefits and potential risks that must be carefully weighed based on the clinical context. While they are highly effective for acute symptom relief in anxiety, seizures, and procedural sedation, their use is associated with a range of adverse effects, particularly with long-term administration or in vulnerable populations. Individualized assessment and cautious prescribing are essential to maximize benefit while minimizing harm. This is because the same neurochemical mechanisms that produce therapeutic relief also underpin the neuroadaptations leading to tolerance and dependence.

Neurobiology of BZD addiction

While the preceding section outlines therapeutic efficacy, prolonged exposure can trigger neuroadaptations that underlie addiction. Although BZDs were initially introduced as a safer alternative to barbiturates, their addictive potential did not become evident until their widespread use [64]. BZDs can induce both reinforcement and physiological dependence, particularly in individuals with underlying vulnerabilities to addiction [39]. *Reinforcement* refers to the psychological factors that motivate continued use, often driven by a drug's rewarding or relief-providing effects, while *physiological dependence* reflects the physical adaptations the body makes in response to chronic exposure [65]. Reinforcement—whether positive (e.g., euphoria) or negative (e.g., relief from anxiety or withdrawal)—plays a key role in learning and maintaining substance use behaviors [65]. In contrast, physiological dependence can lead to tolerance and withdrawal symptoms upon discontinuation, contributing to long-term neurological changes and continued drug use [39].

The mesolimbic dopamine system, particularly dopaminergic neurons in the ventral tegmental area (VTA), plays a key role in the reinforcing effects of many addictive substances [66]. While BZDs do not directly stimulate dopamine release like psychostimulants, they increase dopamine levels via indirect disinhibition. BZDs enhance GABAergic signaling through $GABA_A$ receptors, and BZDs preferentially inhibit GABAergic interneurons that express α1-containing $GABA_A$ receptors in the VTA [67]. This inhibition reduces the tonic GABAergic suppression of dopamine neurons, leading to their disinhibition and subsequent dopamine release in downstream targets such as the nucleus accumbens. This mimics the dopaminergic profile of opioids and cannabinoids [67].

Reinforcement may vary by receptor subunit composition and regional expression. For example, α1 subunits in the VTA are implicated in the rewarding properties of BZDs, whereas α2 subunit-containing receptors in the nucleus accumbens may mediate anxiolysis and contribute to psychological dependence [68, 69]. The mild yet present reinforcing effects likely explain why some individuals escalate BZD use despite medical advice [14].

The primary driver of long-term BZD use, however, is often physiological dependence. With sustained exposure, the GABAergic system undergoes homeostatic adaptations, including downregulation of $GABA_A$ receptors, altered subunit expression, and impaired synaptic inhibition [70]. These changes shift the excitatory-inhibitory balance in the brain, often enhancing glutamatergic transmission during withdrawal, which contributes to symptoms like anxiety, agitation, and seizures [70]. Furthermore, during BZD withdrawal there is an upregulation of AMPA receptor activity, suggesting that excitatory neurotransmission plays a larger role than previously appreciated [71]. This growing excitability, compounded over repeated withdrawal episodes, may intensify symptom severity through a "kindling" effect, where withdrawal effects worsen with each attempt to quit [71, 72]. While withdrawal alone does not define addiction, it can reinforce continued use, especially at critical decision-making points, and contribute to compulsive drug-seeking behavior [70].

Together, these findings underscore that BZD addiction arises from both pharmacological reinforcement via dopaminergic disinhibition and neuroadaptive changes leading to dependence. As such, understanding subunit-specific $GABA_A$ receptor actions in brain regions governing motivation, affect, and stress remains essential for developing safer anxiolytics with reduced abuse potential. These neurobiological insights mirror the population-level patterns of misuse that have emerged over decades of prescribing.

Misuse and public health risks of BZD

Patterns of BZD use and misuse have evolved in parallel with changes in clinical practice, pharmaceutical marketing, and public perception. Historical and contemporary data summarizing global prescribing rates, overdose mortality, and nonmedical use are presented in Table 1. These trends reveal a rapid rise in BZD prescribing during the mid- to late-twentieth century, followed by increasing recognition of dependence and overdose risk that prompted regulatory restrictions and ongoing public-health scrutiny. Aggressive marketing strategies, most notably by Purdue Pharma and its affiliates, fueled early sales growth and contributed to widespread availability [73]. Although Purdue is more widely associated with opioid overpromotion, its earlier benzodiazepine campaigns employed similar tactics: emphasize safety, underplay dependence, and target general practitioners [73, 74]. This helped normalize chronic BZD prescribing and blurred the line between appropriate use and overuse. These marketing legacies highlight how commercial incentives can distort prescribing culture and patient expectations, embedding long-term use within standard psychiatric care.

From the 1990s onward, BZD use expanded across diverse populations and was increasingly linked to adverse outcomes, especially when co-administered with opioids. The intersection of BZD and opioid prescribing has since emerged as a critical driver of overdose mortality, reinforcing calls for cautious co-prescription and enhanced provider education [65, 75]. Inappropriate or prolonged prescribing remains common, particularly among older adults, where risks of cognitive impairment, falls, and sedation are amplified; these patterns informed inclusion of BZDs in the Beers Criteria for potentially inappropriate medications [76, 77]. Additionally, demographic trends highlight sex-based differences in misuse: although men and women report similar overall rates, women more often use BZDs to manage emotional distress and are more likely to engage in non-oral administration routes [78]. Collectively, these findings underscore the need for balanced prescribing practices that preserve short-term therapeutic benefit while mitigating long-term harm through monitoring, patient education, and deprescribing initiatives.

Contemporary BZD prescribing and regulation

In response to the growing misuse and associated mortality described above, efforts to mitigate BZD-related risks have evolved through successive waves of regulation, clinical guidance, and public awareness. Regulatory oversight began with the Controlled Substances Act (CSA) of 1970, which classified BZDs as Schedule IV substances, indicating a relatively low abuse potential compared with Schedules I–III [79]. Yet the adequacy of this classification has been questioned; a 2022 randomized controlled trial found that many U.S. psychiatrists' perceptions of psychoactive drug risk were inconsistent with CSA scheduling designations [80].

Prescribing patterns have shifted markedly in recent years. According to IQVIA data, BZD prescribing has declined across all age groups since 2016, with the sharpest reductions in individuals under 65, although these metrics do not account for illicit use or designer analogs that remain a public-health concern [19]. Additional regulatory interventions include the U.S. Food and Drug Administration's 2016 and 2020 black-box warnings, which emphasized the risks of sedation, respiratory depression, and fatal overdose, particularly when combined with opioids. These warnings urged clinicians to limit duration, use the lowest effective dose, and implement gradual tapering upon discontinuation [81].

While these actions have prompted greater caution, ongoing challenges persist in aligning provider perceptions, addressing patient dependence, and balancing legitimate need with public-safety goals [82]. The broader clinical implementation of deprescribing and tapering frameworks (as outlined in *Treatment Duration, Tapering, and Clinical Practice Implications*) reflects how regulatory guidance now intersects with individualized care. Continued education, interdisciplinary collaboration, and the integration of behavioral supports remain essential to sustaining safe BZD prescribing and discontinuation practices. While policy has shaped prescribing behavior, genetics and metabolism also determine how individuals respond to BZD therapy.

Genetic variability in metabolism and risk of BZD use disorder

Beyond behavioral and regulatory interventions, biological factors also shape individual susceptibility. Pharmacogenetics (PGx) and genome-wide association studies (GWAS) offer promising avenues for understanding the biological underpinnings of BZD misuse and use disorder. PGx focuses on how genetic variation influences individual responses to medications, including the metabolism and clinical effects of BZDs, where several gene-drug associations have been identified with clinical relevance [83]. One key area of study has been the cytochrome P450 liver enzymes, particularly *Cyp2c19* and *Cyp3a4*, which are responsible for metabolizing many BZDs [84]. For instance, individuals carrying loss-of-function variants in *Cyp2c19* are considered poor metabolizers (PMs), leading to elevated levels of norclobazam, the active metabolite of clobazam, and increasing the risk of side effects such as sedation, nausea, and drowsiness [85]. As a result, the FDA has issued specific dosing guidelines for clobazam in *Cyp2c19* PMs, recommending a reduced starting dose of 5 mg/day with careful

up-titration [84]. Similar precautions apply to diazepam, where reduced *Cyp2c19* activity may also necessitate dose adjustments and increased monitoring [84].

Other BZDs, such as alprazolam and phenazepam, are more closely tied to *Cyp3a4* activity. In patients with comorbid anxiety and alcohol use disorder (AUD), studies have shown an inverse relationship between *Cyp3a4* function and phenazepam plasma levels, implicating polymorphisms like *Cyp3a4*22* in variable drug efficacy and side effect profiles [86–89]. However, unlike *Cyp2c19*, no broad FDA dosing recommendations currently exist for *Cyp3a4* variants. There is a growing appreciation for the role of PGx in psychiatry and along with evidence-based guidelines for incorporating *Cyp2d6* and *Cyp2c19* genotyping into clinical practice, including for BZD prescribing [84].

While much PGx work has focused on drug metabolism, understanding the genetic contributions to BZD use disorder specifically requires investigation into the neurobiological targets of BZDs. Since BZDs act by enhancing $GABA_A$ receptor signaling, genes encoding these receptors are of particular interest. Several GWAS have identified polymorphisms in $GABA_A$ receptor subunit genes—particularly *Gabra2*—that are associated with alcohol use disorder (AUD), a condition that shares overlapping neural circuitry with BZD misuse [90, 91]. These findings suggest that similar variants may play a role in susceptibility to BZD use disorder, although this has yet to be firmly established. Additionally, substance use disorders are complex and polygenic, often involving multiple neurotransmitter systems including dopamine, glutamate, serotonin, acetylcholine, endocannabinoids, and endogenous opioids [92]. Variants across these systems may interact in ways that influence the risk for BZD use disorder, though specific genetic markers remain undefined [93].

Importantly, genetic variation in both hepatic metabolism (e.g., *Cyp2c19*, *Cyp3a4*) and neural targets (e.g., *Gabra2*) contributes to interindividual differences in benzodiazepine (BZD) pharmacodynamics and risk for misuse [91, 94]. *Cyp2c19* poor metabolizers exhibit slower clearance and heightened sedation risk, whereas ultrarapid metabolizers may require closer monitoring for breakthrough symptoms or withdrawal [95]. Similarly, *Gabra2* polymorphisms, linked to altered $GABA_A$ receptor function and reward sensitivity, may increase vulnerability to dependence, particularly with high-potency, short-acting agents [92]. Recognizing these genetic factors can help identify individuals at higher risk for adverse effects or overuse, informing safer prescribing and closer follow-up.

Treatment duration, tapering, and clinical practice implications

Building on emerging pharmacogenetic and regulatory insights, appropriate BZD prescribing begins with a clearly defined treatment window and an explicit plan for reassessment. Current deprescribing frameworks emphasize limiting initial BZD use to short-term courses, typically two to four weeks, for acute anxiety, insomnia, or seizure management, after which continued use should be justified by persistent indication and functional benefit [47]. Longer-term therapy may be appropriate in narrowly defined circumstances such as refractory epilepsy, catatonia, or palliative care, but requires structured monitoring for cognitive impairment, psychomotor slowing, and tolerance [9, 47]. Evidence shows that clinicians who establish discontinuation goals at the onset of therapy are significantly more likely to achieve successful deprescribing within six months, underscoring the importance of expectation-setting and follow-up scheduling at initiation [96, 97].

Best-practice tapering strategies strike a balance between pharmacologic precision and behavioral support. Gradual reduction, typically 10–25% of the total daily dose every one to two weeks, remains the standard of care, with longer schedules (up to six months) favored for chronic users or those on high-potency short-acting BZDs such as alprazolam [97]. Converting to an equivalent dose of diazepam or clonazepam allows for smaller decrements and smoother pharmacokinetic transitions [96]. Adjunctive interventions, including CBT, sleep-restriction therapy, and mindfulness-based stress reduction, significantly improve long-term abstinence rates and patient comfort [98]. Case evidence also supports temporary use of melatonin or gabapentinoids for withdrawal-related insomnia and anxiety, and a single-dose phenobarbital bridging strategy has demonstrated success in managing acute withdrawal crises in inpatient settings [96, 97].

Case 1 Outpatient Taper in Anxiety Disorder. A 46-year-old woman with generalized anxiety disorder had been taking alprazolam 1 mg three times daily for two years. After discussing her goals, her psychiatrist initiated a cross-taper to diazepam 15 mg daily and then reduced the dose by 2.5 mg every two weeks, paired with weekly CBT sessions targeting catastrophic thinking and sleep hygiene. Mild rebound anxiety occurred at week six but resolved with behavioral interventions. At 20 weeks, she had discontinued BZDs entirely and remained symptom-free at one-year follow-up [97].

Case 2 Deprescribing in an Older Adult. A 74-year-old man had used temazepam nightly for 15 years to manage chronic insomnia. Following a fall-related hip frac-

ture, a geriatric pharmacist initiated a 10% biweekly taper combined with nonpharmacologic insomnia therapy and caregiver education. By week 14, the patient was BZD-free, with improved alertness, steadier gait, and stable sleep efficiency as verified by actigraphy. This case exemplifies guideline-supported deprescribing in older adults, as outlined in the *Canadian Family Physician* 2018 guideline and Beers Criteria recommendations [47].

Case 3 Inpatient Management of Severe Dependence. A 19-year-old with BZD use disorder after consuming illicit clonazolam purchased online presented with confusion and tremors consistent with withdrawal. He underwent stabilization with phenobarbital loading (10 mg/kg) and was transitioned to diazepam tapering over six weeks, accompanied by motivational interviewing and structured outpatient follow-up. Six months post-discharge, he maintained abstinence and re-engaged in college coursework. This case highlights the importance of interdisciplinary management, linking pharmacologic stabilization with psychosocial rehabilitation, particularly in the context of designer BZD exposure among adolescents and young adults [18, 64].

Emerging pharmacogenetic data suggests that individual genetic profiles may inform tapering and dosing strategies. For instance, patients with *Cyp2c19* loss-of-function variants metabolize diazepam and clobazam more slowly, warranting lower initial doses and longer taper intervals to minimize sedation and withdrawal rebound [82]. Conversely, those with ultrarapid metabolism may benefit from more gradual dose adjustments to avoid subtherapeutic exposure [82]. Likewise, *Gabra2* variants associated with enhanced reward sensitivity could guide clinicians toward longer-acting BZDs, adjunctive behavioral support, and closer monitoring during discontinuation [99]. Integrating pharmacogenetic screening into deprescribing frameworks could thus individualize therapy, reducing adverse events and improving long-term success of BZD withdrawal. Together, these frameworks, from molecular understanding to clinical management, underscore the need for integrated, patient-centered strategies.

Conclusions: integrating knowledge for safer use of BZDs

Benzodiazepines occupy a unique position in modern pharmacology— highly effective for acute symptom management in anxiety, seizures, and procedural sedation, yet associated with substantial risks of dependence, misuse, and overdose, particularly with long-term or inappropriate prescribing. This review traced the historical development and mechanisms of BZDs, from their emergence as safer alternatives to barbiturates to their current clinical utility across psychiatric and neurologic conditions. The pharmacological foundation of BZDs, modulation of $GABA_A$ receptors, explains both their therapeutic efficacy and their potential for abuse through reinforcement and physiological dependence. These neurobiological mechanisms, combined with sociocultural factors such as pharmaceutical marketing and prescribing norms, have contributed to the persistence of misuse, especially among elderly patients, women, and individuals with co-occurring substance use disorders. The opioid crisis has further highlighted the dangers of BZD co-administration, underscoring the need for evidence-based prescribing and structured discontinuation strategies.

Research priorities should focus on integrating pharmacogenomic and GWAS to identify genetic variants influencing BZD metabolism, efficacy, and vulnerability to substance use disorders. Understanding how variants such as *CYP2C19* and *GABRA2* affect metabolism and reward sensitivity could enable personalized approaches to prescribing, tapering, and withdrawal management. Translating these genetic insights into clinical algorithms represents a key step toward precision psychiatry for BZD therapy.

Clinically, BZD use should be restricted to short-term indications, with structured plans for reassessment and gradual tapering supported by behavioral interventions such as CBT mindfulness-based stress reduction, and sleep hygiene education. Caution is warranted in high-risk populations, including geriatric patients and those concurrently prescribed opioids, where fall risk, cognitive impairment, and respiratory depression are magnified. Interdisciplinary care models that combine pharmacologic precision with psychosocial support offer the best opportunity for sustained discontinuation success.

From a policy perspective, greater investment in prescriber education and prescription-monitoring infrastructure is essential. Strengthening oversight of BZD and opioid co-prescribing, incentivizing adherence to evidence-based deprescribing protocols, and promoting access to nonpharmacologic alternatives could help rebalance the risk-benefit profile of these widely used agents. Regulatory frameworks should encourage responsible use while ensuring that patients who genuinely benefit from short-term BZD therapy can access it safely and discontinue it successfully.

Ultimately, mitigating the harms of benzodiazepines will require a unified approach, linking advances in genetics and neurobiology with evidence-based clinical practice and public health policy. By integrating these efforts, the field can move toward a model of care that preserves the therapeutic promise of BZDs while minimizing their perils of misuse.

Abbreviations

AUD	Alcohol use disorder
BZDs	Benzodiazepines

BZ1	BZD receptor 1
BZ2	BZD receptor 2
CBT	Cognitive behavioral therapy
CNS	Central nervous system
CSA	Controlled Substances Act
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GAD	Glutamic acid decarboxylase
GWAS	Genome-wide association studies
IM	Intramuscular
IV	Intravenous
PGx	Pharmacogenetics
PMs	Poor metabolizers
PTSD	Post-traumatic stress disorder
VTA	Ventral tegmental area

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