REVIEW ARTICLE

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Treatment of Benzodiazepine Dependence

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Traditionally, various terms have been used to define substance use–related disorders. These include "addiction," "misuse" (in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition [DSM-IV][1]), "harmful use" (in the *International Classification of Diseases, 10th Revision* [ICD-10][2]), and "dependence."[3] Long-term intake of a drug can induce tolerance of the drug's effects (i.e., increased amounts are needed to achieve intoxication, or the person experiences diminished effects with continued use[4]) and physical dependence. Addiction is defined by compulsive drug-seeking behavior or an intense desire to take a drug despite severe medical or social consequences. The DSM-IV and ICD-10 define misuse and harmful use, respectively, on the basis of various somatic or psychological consequences of substance use and define dependence on the basis of a cluster of somatic, psychological, and behavioral symptoms. According to the ICD-10, dependence is diagnosed if 3 or more of the following criteria were met in the previous year: a strong desire or compulsion to take the drug, difficulties in controlling drug use, withdrawal symptoms, evidence of tolerance, neglect of alternative pleasures or interests, and persistent drug use despite harmful consequences. The latest edition of the DSM (DSM-5)[4] has abandoned the categorical distinction between abuse and dependence in favor of a dimensional approach, specifying 11 criteria for substance-use disorders, which range from mild (in patients meeting 2 or 3 criteria) to severe (in patients meeting 6 or more criteria).

Key elements of substance-use disorders are dose increases, tolerance of and craving for the drug's effects, and loss of control. These diagnostic criteria and definitions are used for all classes of abused drugs, including prescription drugs such as benzodiazepines. However, the criteria may be less appropriate — or even problematic — in the case of mentally ill patients who use or are dependent on prescription drugs than in the case of mentally healthy persons who take drugs primarily for recreational purposes.

BENZODIAZEPINES

PHARMACOLOGIC FEATURES

The first benzodiazepine to be approved and introduced into clinical practice was chlordiazepoxide, which was introduced to the market in 1960.[5,6] Today, approximately 35 benzodiazepine derivatives exist, 21 of which have been approved internationally (www.emcdda.europa.eu/publications/drug-profiles/benzodiazepine).[6] They all bind to specific sites on the γ-aminobutyric acid (GABA) type A ($GABA_A$) receptor, increasing the receptor's affinity for GABA, an inhibitory neurotransmitter (Fig. 1).

The greater affinity of $GABA_A$ receptor for GABA increases the frequency of chloride-channel opening and potentiates the inhibitory effect of GABA in the central nervous system (CNS).[7] Thus, benzodiazepines have no direct agonistic

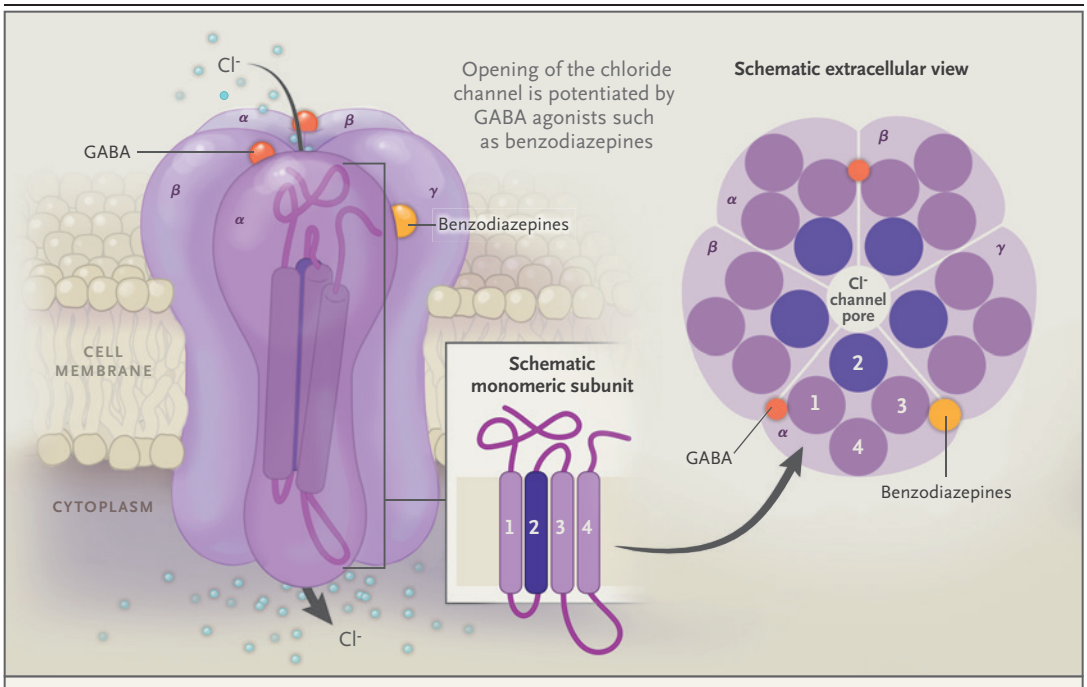

Figure 1. Pharmacologic Characteristics of γ-Aminobutyric Acid Type A ($GABA_A$) Receptors.

The $GABA_A$ receptor consists of five transmembrane glycoprotein subunits arranged around the central chloride channel. Each subunit is composed of four domains (domains 1 through 4); domain 2 (dark purple) is the part of the monomeric subunit that lines the chloride channel. Benzodiazepines increase the affinity of the $GABA_A$ receptor for GABA and the likelihood that the receptor will open for chloride ions (light blue).

effect at the receptor. The $GABA_A$ receptor is composed of various subunits (α_1 through α_6, β_1 through β_3, and γ_1 through γ_3) and variants, with hypnotic agents acting mainly through the α_1 subunit. $GABA_A$ receptor function can be measured by means of positron-emission tomography with specific radiotracers.[8]

Pharmacologically, benzodiazepines cannot be clearly divided into those that are more anxiolytic and those that are more hypnotic. They have completely replaced older hypnotic agents, which were much less safe.[5] Benzodiazepines are well absorbed and are highly protein-bound. They are metabolized in two basic pathways: glucuronide conjugation and microsomal oxidation. Some benzodiazepines already have a hydroxyl group (e.g., oxazepam and lorazepam) and consequently are metabolized directly by glucuronide conjugation; this group tends to have a shorter elimination half-life. However, the majority of benzodiazepines are demethylated or oxidized before conjugation and therefore have a longer half-life, with an associated risk of accumulation. Many benzodiazepines have pharmacologically active metabolites. Table 1 shows the half-lives of major benzodiazepines and relevant metabolites.[6,9,10] Short-acting benzodiazepines are typically used as hypnotic agents (e.g., triazolam), and longer-acting benzodiazepines as anxiolytic or anticonvulsant agents (e.g., diazepam and clonazepam). There is modest evidence that benzodiazepines with a shorter half-life are associated with a greater risk of dependence.[11] Benzodiazepines also potentiate the sedative effects of opiates.[6]

CLINICAL USE

Benzodiazepines can be divided into anxiolytic agents and hypnotic agents on the basis of their clinical effects. In principle, however, all benzodiazepines have anxiolytic, hypnotic, muscle-relaxant, anticonvulsant, and amnesic effects. They are used as sedatives and to treat withdrawal symptoms, including alcohol withdrawal delirium.[12,13] Benzodiazepines are relatively safe for short-term use (2 to 4 weeks), but their safety has not been established beyond that period,[5] and dependence develops in approximately half

of patients who use benzodiazepines for longer than 1 month.[11] The risk of fatal intoxication by the use of a single drug is low.

SIDE EFFECTS

The main disadvantages and dose-dependent side effects of benzodiazepines are drowsiness, lethargy, fatigue, excessive sedation, stupor, "hangover effects" the next day, disturbances of concentration and attention, development of dependence, symptom rebound (i.e., recurrence of the original disorder, most commonly a sleep disorder) after discontinuation, and hypotonia and ataxia.[14-17] Benzodiazepines can seriously impair driving ability and are associated with increased risks of traffic accidents, as well as falls and fractures.[18-20]

Patients with myasthenia gravis, ataxia, the sleep apnea syndrome, chronic respiratory insufficiency, spinal and cerebellar ataxia, angle-closure glaucoma, or acute CNS-depressant intoxication should not receive treatment with this class of drugs. Paradoxical reactions are not uncommon in older patients (>65 years of age). Psychomotor retardation and cognitive dysfunction (memory loss, lack of concentration, and attention deficits) may occur.[15,21,22] These drugs are not recommended for the treatment of insomnia, agitation, or delirium in the elderly and, if prescribed in this population, should be restricted to short-term use.[23] Their amnestic effects can result in memory gaps, especially at higher doses.[14] An association of long-term benzodiazepine use with brain atrophy and dementia is controversial.[17]

Table 1. Pharmacologic Classification and Half-Lives of Representative Benzodiazepines.*

Benzodiazepine	Substance Half-Life	Metabolite Half-Life
	hours	
Hypnotic agents		
Long half-life: flurazepam	2–3	≤100
Intermediate half-life		
Flunitrazepam	10–30	20–30
Nitrazepam	18–30	—
Short half-life		
Brotizolam	3–6	3–6
Lormetazepam	8–14	8–14
Temazepam	7–14	4–15
Very short half-life: triazolam	1.5–5	—
Anxiolytic agents		
Long half-life		
Diazepam	24–48	≤200
Chlordiazepoxide	6–38	≤200
Clobazam	50	20
Clorazepate dipotassium	2–2.5	≤200
Medazepam	2–2.5	≤200
Prazepam	1–3	≤200
Short-to-intermediate half-life with active metabolites		
Lorazepam	2	—
Oxazepam	30	—
Alprazolam	12–15	1
Bromazepam	15	6

* Data on hypnotic agents are from Soyka,[6] Benkert and Hippius,[9] and Julien,[10] and data on anxiolytic agents are from Benkert and Hippius.[9] Dashes denote no active metabolite.

BENZODIAZEPINE DEPENDENCE

NEURAL CORRELATES

The ventral tegmental area and nucleus accumbens are parts of the mesolimbic area of the brain; drugs that cause dopamine release in these areas generally have addictive potential.[24,25] Neural projections to the prefrontal cortex represent important connections in the "addiction network." The landmark studies by Tan et al.[26] showed that benzodiazepines also activate dopaminergic neurons in the ventral tegmental area by modulating $GABA_A$ receptors in neighboring interneurons. The special relevance of α_1-containing $GABA_A$ receptors in the ventral tegmental area has been noted.[26] This information makes it clear that benzodiazepines act through mechanisms similar to those of other drugs of abuse.

EPIDEMIOLOGIC FEATURES

The number of benzodiazepine prescriptions in the United States increased substantially from 1996 to 2013.[27] Deaths from overdose also increased, by a factor of more than 4 (from 0.58 to 3.07 deaths per 100,000 adults),[27] with a plateau after 2010, but nearly all the deaths involved the use of other substances in addition to benzodiazepines. Of patients receiving opioid maintenance therapy, approximately 46 to 71% use benzodiazepines[28,29] (44% of German patients[30]). These drugs enhance the respiratory-depressant

effects of opioids. On August 31, 2016, the Food and Drug Administration issued a drug-safety communication about serious risks, including death, when opioid pain or cough medicines are combined with benzodiazepines. The safety announcement warned that "health care professionals should limit prescribing opioid pain medicines with benzodiazepines . . . only to patients for whom alternative treatment options are inadequate."[31]

In contrast to the prescribing pattern in the United States, the prescription of benzodiazepines in Europe has decreased substantially over the past few years. Nevertheless, benzodiazepines are still among the most frequently used psychopharmaceuticals worldwide. Long-term use is not synonymous with dependence. Recent data show that 35.8% of patients with new benzodiazepine prescriptions continue to use the drug after 3 months, with 15.2% using it for 1 year, and 4.9% for 8 years; 3% of the general population uses benzodiazepines for the long term.[32] There is no standard definition of long-term use, but the most common definition is 6 to 12 months.[33] The risk of dependence on benzodiazepines or so-called z-drugs (nonbenzodiazepine drugs that have effects that are similar to those of benzodiazepines and most of which have generic names that start with the letter z [e.g., zolpidem, zopiclone, and zaleplon]) is significantly associated with a history of mental illness and with a large quantity of drugs taken.[34] The use of z-drugs has increased in Germany during the past 20 years, which is thought to have compensated in part for the decrease in benzodiazepine use.[35]

According to an epidemiologic study,[36] 2.3 million people in Germany are dependent on medications; on the basis of DSM-IV criteria, the estimated overall prevalence of sedative abuse is 0.8% (among both men and women), and the prevalence of dependence is 1.4% among men and 1.3% among women. Benzodiazepine use tends to increase significantly with age.[37,38] Petitjean et al.[38] reported that in Switzerland, 14.5% of patients were given benzodiazepines for more than 12 months. Neutel[39] found misuse of these drugs in 4.1% of the Canadian population. In the United States, Huang et al.[40] reported an abuse rate of 1.1% for sedatives and 1.0% for tranquilizers from this drug family.

A retrospective study of 2008 data in the United States showed that 5.2% of persons between the ages of 18 and 80 years used benzodiazepines, as did 8.7% of those between the ages of 65 and 80 years.[37] Women used benzodiazepines twice as frequently as men did. Long-term use was shown in a quarter of the sample. Moore et al.[41] recommend stricter controls and suggest that benzodiazepines should be prescribed only by psychiatrists, who give fewer long-term prescriptions than other physicians; however, the issue is controversial. There is a striking discrepancy between the high prevalence of benzodiazepine dependence and the very low treatment rates, especially in addiction service centers.[42]

CLINICAL FEATURES

In a study reported in 1961, Hollister et al. switched mentally healthy persons from chlordiazepoxide (300 to 600 mg) to placebo and found that sudden withdrawal resulted in seizures, delirium, and psychosis.[43] A special characteristic of benzodiazepines is that physical and mental dependence can develop in the absence of tolerance (low-dose dependence). Typical behavioral features of benzodiazepine dependence include doctor-shopping (i.e., seeking prescriptions from several different providers), obtaining prescriptions from different pharmacies, and overlapping prescriptions (Table 2).[6,44-46] A recent study showed that clinical correlates of long-term benzodiazepine use are older age (>65 years), prescription by a psychiatrist, regular use, use of a high dose, and concomitant prescription of psychotropic drugs.[44]

WITHDRAWAL SYMPTOMS

Symptoms of withdrawal after long-term benzodiazepine use usually develop faster with shorter-acting agents (within 2 to 3 days) than with longer-acting agents (within 5 to 10 days). Most withdrawal symptoms are associated with a state of brain hyperexcitability and can be divided into physical, psychological, and sensory symptoms. The mildest form of withdrawal is symptom rebound and is particularly common with withdrawal from benzodiazepines that are used for sleep disorders. The most common physical symptoms of withdrawal are muscle tension, weakness, spasms, pain, influenza-like symptoms (e.g., sweating and shivering), and "pins and needles." The most common psychological withdrawal symptoms are anxiety and panic disorders, rest-

Table 2. Behavioral Correlates of Benzodiazepine Dependence.*

People who have become dependent on therapeutic doses of benzodiazepines usually have several of the following characteristics:
They have taken benzodiazepines in prescribed "therapeutic" (usually low) doses for months or years.
They have gradually come to "need" benzodiazepines to carry out normal, day-to-day activities.
They have continued to take benzodiazepines even though the original indication for the prescription has disappeared.
Because of withdrawal symptoms, they have difficulty stopping use of the drug or reducing the dose.
Those taking short-acting benzodiazepines have anxiety between doses or a craving for the next dose.
They contact their doctor regularly to obtain repeat prescriptions.
They become anxious if the next prescription is not readily available; they may carry their tablets around with them and may take an extra dose before an event that is anticipated to be stressful or before spending the night in a strange bed.
They may have increased the dosage since the original prescription.
They may have anxiety symptoms, panic attacks, agoraphobia, insomnia, depression, or increasing physical symptoms, despite continuing to take benzodiazepines.
Doctor-shopping, emergency visits, and lost prescriptions are common.
They use private prescriptions rather than those for which the cost would be reimbursed by health insurance.
They take hypnotic agents during the day.

* Data are from Soyka,[6] Ashton,[45] and Soyka et al.[46]

lessness and agitation, depression and mood swings, psychovegetative symptoms (e.g., tremor), reduced concentration, and sleep disturbances and nightmares.[6,45-49] Appetite loss, tachycardia, blurred vision, and dry mouth may also be present, as may tinnitus, drowsiness, or derealization (a feeling that one's surroundings are not real). Disorders of perception are relatively common and range from hyperacusis to photophobia to dysesthesia; these symptoms are not pathognomonic but are characteristic of benzodiazepine withdrawal. Seizures are quite common, especially if the agent is discontinued abruptly. Severe withdrawal symptoms include paranoid thoughts, hallucinations, depersonalization, and withdrawal delirium. Tables 3 and 4 provide an overview of withdrawal symptoms.[6,45,47,49]

TREATMENT

TREATMENT OF WITHDRAWAL SYMPTOMS

Numerous studies and a Cochrane review have examined treatment of withdrawal.[50-52] The overall consensus is that benzodiazepines should be discontinued gradually over a period of several weeks (e.g., 4 to 6 weeks or more for diazepam doses >30 mg per day), to prevent seizures and avoid severe withdrawal symptoms. The withdrawal rate is often determined by a person's capacity to tolerate symptoms.[53] Recommendations range from reducing the initial benzodiazepine dose by 50% every week or so[6] to reducing the daily dose by between 10% and 25% every 2 weeks.[53] A period of 4 to 6 or 4 to 8 weeks is suitable for withdrawal for most patients. If possible, prolonged reductions over a period of many months should be avoided in order to prevent the withdrawal treatment from becoming the patient's "morbid focus."[15]

Whether switching to a long-acting agent such as diazepam has fundamental advantages is unclear,[45] as is the question of whether hospital admission is required for a "blind reduction" (i.e., the patient is not told the exact dose). The use of several benzodiazepines should be converted to the use of one, preferably diazepam. Withdrawal from short-acting benzodiazepines is associated with higher dropout rates than withdrawal from longer-acting agents,[6,51] but switching from a drug with a short half-life to one with a longer half-life is not associated with a better outcome.[6,51] A relatively fixed withdrawal schedule with a precise duration of withdrawal treatment is recommended. Withdrawal is sometimes successful on an outpatient basis, but patients should be hospitalized for withdrawal from very high doses (a dose equivalent to ≥100 mg of diazepam daily).

Table 3. Clinical Symptoms and Complications of Benzodiazepine Withdrawal.*

Psychopathologic symptoms
Increased anxiety
Nervousness
Sleep disorders
Inner restlessness
Depressive symptoms
Irritability
Psychosis-like conditions, delirium
Depersonalization and derealization
Confusion
Vegetative symptoms
Trembling
Sweating
Nausea and vomiting
Motor agitation
Dyspnea
Increased heart rate
Elevated blood pressure
Headaches
Muscle tension
Neurologic and physical complications
Increased risk of seizures
Impairment of voluntary movements
Cognitive impairments
Impairment of memory
Pronounced perceptual impairments
Hyperacusis
Photophobia
Hypersomnia
Dysesthesia, kinesthetic disorders, muscle twitching and fasciculations

* Data are from Soyka,[6] Ashton,[45] Lader and Kyriacou,[47] and Soyka and Batra.[49]

In patients receiving opioid maintenance therapy, the dose of the opioid (e.g., methadone) should be kept stable throughout the benzodiazepine-reduction period and high enough to prevent symptoms of opioid withdrawal.[29] In cases of very high methadone doses (>150 mg per day) and frequent intoxicated presentations, the dose may be decreased.[29] The partial opioid agonist buprenorphine may carry a lower risk of benzodiazepine-related overdose than a full agonist (e.g., methadone).[29,54] Concurrent opioid detoxification is not recommended.[53] For some patients with concomitant benzodiazepine (or alcohol) use, the opioid is underdosed, and the opioid dose should be adjusted in these patients to relieve them from opioid-withdrawal symptoms.

Concomitant psychopharmacotherapy for benzodiazepine withdrawal is symptom-oriented and pragmatic. No medication is approved for the treatment of benzodiazepine-use disorders, and only a handful of relevant studies have been published. In patients with a coexisting psychiatric disorder (depression, anxiety, or schizophrenia), integrative therapy programs addressing both the underlying psychiatric condition and the benzodiazepine use are recommended.[6]

Only a few evidence-based treatment recommendations for pharmacotherapy are available.[15,51] Symptomatic treatment includes antidepressant agents for depression and sleep problems, as well as mood stabilizers, especially carbamazepine (200 mg twice per day), although empirical evidence for these approaches is limited.[5,47,51] Alternatives are nonbenzodiazepine anxiolytic agents, pregabalin, gabapentin, and beta-blockers[6,55]; nonbenzodiazepine hypnotic agents are additional options. The abuse potential of GABAergic compounds such as pregabalin must be kept in mind.[6] In the case of a chronic sleep disorder, recommended medications include such antidepressants as trazodone (at a dose of 25 to 150 mg per day), doxepin (10 to 150 mg per day), mirtazapine (7.5 to 30 mg per day), and trimipramine (10 to 150 mg per day), which should be given 1 to 3 hours before bedtime. These agents act mainly by antagonism at the histamine H_1 receptor and in part by anticholinergic actions and have no apparent abuse potential.[48] Alternatives are antihistaminergic agents, most of which are over-the-counter medications and include diphenhydramine (25 to 50 mg per day), doxylamine (25 to 50 mg per day), hydroxyzine (37.5 to 75 mg per day), and promethazine (25 to 200 mg per day).[48] Antidepressants that act primarily through serotonin-reuptake inhibition may be more suitable for patients with anxiety disorders. There is very modest evidence that melatonin improves sleep during benzodiazepine withdrawal, but its use remains largely experimental,[47,56,57] as does the use of a slow subcutaneous infusion of the benzodiazepine antagonist flumazenil.[58] However, flumazenil use carries substantial med-

Table 4. Differential Diagnosis of Severe Benzodiazepine Withdrawal Syndromes or Intoxication.*

Alcohol, drug intoxication
Intoxication from other psychotropic substances (polydrug use)
Hypoglycemia
Epilepsy
Cerebral hemorrhage
Cerebral infarction or brain injury
Myocardial infarction
Metabolic disturbances (e.g., thyroid disorder)
Psychosis, mania, or bipolar disorder
Alcohol-withdrawal delirium
Delirium in the elderly or in people with serious medical conditions
Agitation associated with psychopathy

* Data are from Soyka,[6] Ashton,[45] Lader and Kyriacou,[47] and Soyka and Batra.[49]

ical risks (e.g., seizures and psychoses).[47] A kind of "benzodiazepine substitution" with slow-onset, long-acting benzodiazepines has also been discussed,[59] but clinical evidence supporting its use is lacking.

PSYCHOTHERAPY FOR BENZODIAZEPINE DEPENDENCE

Minimal, brief interventions in primary care (provision of simple advice and informational leaflets) can facilitate an initial reduction in benzodiazepine use.[60,61] A form of psychoeducation (i.e., provision of information on the effects and risks of long-term benzodiazepine use and possible alternatives) is often the initial step in treatment[60] but should be accompanied by other psychosocial interventions. Psychotherapeutic interventions for long-term benzodiazepine use have three goals: facilitate the withdrawal itself, facilitate further abstinence, and treat the underlying disorder.[15]

A number of evidence-based treatments are available for substance use in general.[3,6,62] For example, techniques based on the transtheoretical model of Prochaska and Velicer,[63] such as motivational interviewing,[64] aim to induce behavioral changes by helping patients to balance and reconsider the advantages and disadvantages of drug use and motivating them to discontinue use. Higher self-efficacy expectations and a stronger belief in the ability to quit are associated with a better outcome.[60] However, little evidence is available for psychosocial interventions in people with both severe illness and substance misuse,[65] and only a few experimental studies have investigated the efficacy of various therapies for prescription-drug dependence.[66,67]

Cognitive behavioral therapy plays a strong role in treating benzodiazepine dependence.[15] This therapeutic approach encompasses a number of techniques and combines elements of learning and behavioral theory. Cognitive behavioral therapy supports direct changes, addresses psychosocial stress factors, and provides training in coping and social skills and in the management of risk situations for benzodiazepine use (relapse prevention). The therapeutic components include social-competence training, relaxation techniques, training to overcome anxiety, and other behavioral-therapy approaches. These components focus on the reasons for and experiences with medication use and how to deal with risk situations and anxiety about meeting expectations and may also address pathogenic relationship patterns and unresolved mental conflicts. Cognitive behavioral therapy is the most widely used treatment for benzodiazepine dependence,[68] although a randomized, controlled trial showed that a 15-month period for tapering off benzodiazepines under controlled conditions without psychotherapy was superior to usual care alone or in combination with cognitive behavioral therapy.[67] In this study, short-term abstinence rates were 29 to 36%, but the 10-year abstinence rate was 59%.[69]

Most meta-analyses of psychotherapy for substance-use disorders focus on alcohol or "illegal" drugs.[70] Psychological interventions with stepwise withdrawal are more effective than standard treatment (routine care),[71] and short-term interventions performed by a family physician are helpful.[61] A recent Cochrane analysis of psychosocial interventions for benzodiazepine use and dependence included 25 studies involving a total of 1666 people.[50] Two analyses were performed: one assessed the effectiveness of cognitive behavioral therapy plus benzodiazepine tapering versus tapering alone, and the other examined motivational interviewing versus treatment as usual. In brief, the analyses showed that cognitive behavioral therapy plus tapering is effective in reducing benzodiazepine use over a short

(3-month) period but not at 6 months or later and that there is insufficient evidence to support the use of motivational interviewing to reduce benzodiazepine use.

In general, the prognosis for patients who undergo withdrawal treatment for benzodiazepine dependence is fairly good.[6] However, additional therapeutic approaches may be necessary, depending on whether there is underlying mental illness.[49] Motivational techniques are particularly useful during inpatient withdrawal treatment, whereas individual or group psychotherapeutic techniques are more useful during outpatient withdrawal treatment (e.g., for low-dose dependence). Other interventions include self-control training, cue exposure focusing on settings that may induce a craving for benzodiazepines, marital and family therapy, and less frequently, psychodynamically oriented treatments that focus on underlying conflicts and deficits in ego and personality development. Twelve-step treatments are frequently used in the United States, but they are less common in other parts of the world and are rarely used for benzodiazepine dependence.

Many treatments are eclectic, combining elements from various therapeutic approaches. Removal of self-medication as a rationalization for benzodiazepine use is of great relevance, especially for patients with a coexisting psychiatric disorder, such as anxiety disorder.[72] More psychodynamically and psychoanalytically oriented therapies interpret medication dependence as a failed attempt at self-healing. These therapies address frustration, poor problem-solving strategies, and failure to tolerate negative emotions, all of which generally play a large role in drug dependence. Systemic therapies focus on the patient as the symptom carrier in a disturbed or dysfunctional family system and view addiction behavior as an attempt to regulate or control relationships. Psychoeducation includes provision of information on the effects and side effects of medications. In addition, self-control techniques are offered.

Nonpharmacologic interventions, especially stimulus control and sleep restriction, and to a lesser extent, sleep-hygiene education (which teaches patients to maintain a regular wake-and-sleep pattern, relax regularly during the week, and avoid stimulants and large meals before bedtime, among other things), are effective for insomnia in general.[73] They can also be used for sleep disorders associated with benzodiazepine withdrawal. One study showed that interventions such as sleep assessment, basic sleep hygiene (going to bed at the same time every night and avoiding naps), stimulus control (a quiet, comfortable bedroom, with no television viewing in bed and no lights), behavioral therapies such as sleep-restriction procedures (which force the patient's available sleep time into a fixed window), relaxation techniques such as progressive muscle relaxation, and cognitive treatments were effective for insomnia during long-term hypnotic-drug use, with results persisting for more than 1 year.[74]

PREVENTION OF DEPENDENCE

A recent systematic review of patients' experiences with and perceptions of benzodiazepine use and use of other hypnotic agents identified themes of relevance for safer prescribing of these drugs, including the effects of insomnia and failed self-care strategies, among others.[75]

Treatments lasting 2 to 3 months or more and marked dose increases should be avoided. In some patients, especially those with sleep disorders, intervals of treatment rather than continuous treatment may be advisable. Careful evaluation and reevaluation of the indication for treatment, adherence to dosing, avoidance of multiple prescriptions, and timely discontinuation of treatment (usually within 4 to 6 weeks) are essential. High-risk groups include persons who are alcohol- and drug-dependent, are chronically ill (particularly those with pain syndromes), or have chronic sleep disorders, personality disorders, or dysthymia. A critical issue is avoiding long-term prescriptions for older patients in the absence of a clear target symptom.

CONCLUSIONS FOR CLINICAL PRACTICE

There are clear and evidence-based treatment standards for medication withdrawal in benzodiazepine-dependent patients, even though they are a heterogeneous group. Table 5 presents a brief synopsis of treatment standards. In psychotherapy, good evidence exists for cognitive behavioral therapy and motivational approaches and for providing information and psychoeduca-

Table 5. Management of Benzodiazepine (BZD) Withdrawal.

Situation	Treatment Approach	Level of Evidence
Approach to BZD dependence in general	Gradual withdrawal over a period of several weeks or months	High
Use of several BZDs or sedatives	Switch to use of only one BZD for detoxification (diazepam)	Good
Choice of BZD for detoxification	Switch to a long-acting BZD (diazepam)	Low
BZD withdrawal in a patient receiving opioid maintenance therapy	Adjustment of opioid dose to prevent opioid withdrawal; switch to a partial agonist (buprenorphine)	Good for adjustment of opioid dose; moderate for switch to partial agonist
Concomitant pharmacotherapy for BZD withdrawal	Carbamazepine, 200 mg twice a day	Moderate
Sleep disorders	Antidepressants, antihistaminergic drugs, melatonin; improved sleep hygiene, sleep restriction, relaxation techniques	Moderate
Other drugs for treatment of withdrawal symptoms	Pregabalin, gabapentin, beta-blockers; flumazenil	Low for pregabalin, gabapentin, and beta-blockers; experimental for flumazenil
Psychotherapy	Cognitive behavioral therapy and other approaches	Good

tion. The prognosis with standard treatment is often fairly good. At the same time, from a clinical perspective, one does not have to attempt benzodiazepine withdrawal in every case. For patients without any motivation for withdrawal and those with a severe depressive episode or other major mental disorder, stabilization may be warranted before initiating withdrawal treatment. If patients have severe psychopathological symptoms, one can refrain from attempting withdrawal, given that the process often lasts for weeks and is sometimes distressing for the patient and the physician. Also, withdrawal can be difficult to achieve in some elderly persons with long-term, low-dose dependence on hypnotic agents. If complete discontinuation of benzodiazepines is unlikely, one can attempt to reduce the dose as a harm-reduction strategy. Additional studies on adequate pharmacotherapy during and after benzodiazepine withdrawal and more evidence-based strategies clearly are required.

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