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REVIEW YJBM

Prescription Sedative Misuse and Abuse

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Sedatives are widely prescribed for anxiety or insomnia and include benzodiazepines, selective benzodiazepine receptor subtype agonists (z-drugs), and barbiturates. These sedatives are controlled substances due to their potential for misuse and abuse. Misuse is often self-medication (chemical coping) of psychological symptoms in ways unauthorized by the prescriber, usually as dose escalation leading to requests for early refills. Sedatives are abused for euphoric effects, which may have dangerous consequences. Some sedative overdoses can be treated with flumazenil, a reversal agent, along with supportive care. Sedative withdrawal syndrome is treated by tapering the sedative and may require hospitalization. Long-term treatment of sedative addiction requires counseling, often with the help of an addiction-treatment professional.

Sedative medications are widely used for treatment of insomnia and anxiety but have potential for misuse and abuse by patients. This article uses two actual patient cases to illustrate problematic patient behavior with use of prescribed sedatives, and the discussion describes ways that clinicians can effectively deal with sedative abuse and its consequences. It is important to address problematic patient behaviors regarding controlled substance medications such as sedatives for reasons of patient safety (to prevent morbidity and mortality from overdose) and ethical issues such as appropriate treatment of addiction and prevention of drug diversion.

CASE 1

A 50-year-old woman presents for evaluation for anxiety and sleep problems. She has a long history of depression with periodic anxiety attacks. She has been prescribed alprazolam (Xanax) for 5 years for anxiety and sleep problems. She describes episodes of shaking and dyspnea with anxiety lasting for about an hour several times per day for which she would take alprazolam 2-3 mg. For the past 3 months, she has had depressed mood with crying spells, decreased appetite, and weight loss. She has gradually been increasing the amount of alprazolam she takes, up to 7-10 mg per day. She admits to taking more alprazolam than prescribed and denies buying any medications illegally without a prescription ("off the street"). She wants to stop alprazolam because it has been causing memory problems (blackouts) and her physicians have expressed concern about her overuse without much improvement in her depression. However, she feels she needs it and wants something to help her anxiety symptoms and her insomnia. She denies abusing illicit drugs or alcohol (she has one mixed drink per week) and denies suicidal ideation. She is widowed and lives alone, and she has poor coping skills and limited social support. She reports that her alprazolam vanished about a week ago; she was not sure if it was stolen or if she had a blackout from taking it. At that time, she was started on clonazepam (Klonopin), but she states she prefers alprazolam.

TYPES OF ABUSED SEDATIVES

Sedative drugs include benzodiazepines, barbiturates, and other sleeping pills (see Table 1). These are commonly prescribed for insomnia and other sleep problems and are also used for anxiety, either generalized or for panic attacks [1]. The most commonly prescribed

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†Abbreviations: AMTB, aberrant medication-taking behaviors; BZ1, benzodiazepine subtype 1 receptor; BZ2, benzodiazepine subtype 2 receptor; FDA, Food and Drug Administration; GABA, gamma-aminobutyric acid; PDMP, prescription drug monitoring program; SUD, substance use disorder; UDT, urine drug testing.

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sedatives are benzodiazepines [2], which are similar to alcohol in that they facilitate the inhibitory effects of gamma-aminobutyric acid (GABA†) at the GABA-A receptor complex, primarily by binding non-selectively to the benzodiazepine subtype 1 (BZ1) and BZ2 receptors. Some benzodiazepines (oxazepam [Serax], lorazepam [Ativan], and temazepam [Restoril]) are directly conjugated via glucuronyl transferase and then excreted, while others (alprazolam [Xanax] and diazepam [Valium]) are first metabolized by the cytochrome P-450 isozyme 3A4 and/or 3A5 [3]. In addition to reducing anxiety and inducing sleep, benzodiazepines can cause euphoria and, therefore, are subject to abuse as recreational drugs. Flunitrazepam (Rohypnol) is a short-acting benzodiazepine that is available by prescription in South America and Europe but not in the United States; its potency is about 10 times that of diazepam [4]. It has achieved notoriety as a date-rape drug because it is colorless, odorless, and miscible with alcohol (which enhances the sedative and amnestic effects). These properties have made it popular among sexual predators to add to the drink of a potential victim. Many different benzodiazepines are prescribed, with different durations of action, rates of onset, and intensities of euphoria.

In addition to benzodiazepines, there are three non-benzodiazepine drugs approved by the U.S. Food and Drug Administration (FDA) for treatment of insomnia: zaleplon (Sonata), zolpidem (Ambien), and eszopiclone (Lunesta) [5]. These sedatives are often called "z-drugs." They are agonists that bind to the same binding site as benzodiazepines at the GABA-A receptor, but they only act on the BZ1 subtype receptor [6] and, thus, are similar to typical benzodiazepines (i.e., diazepam, alprazolam, and others), even though they are more selective receptor subtype agonists. They possess a shorter duration of action and half-life, do not disturb overall sleep architecture, and cause less residual effects during daytime hours, making them more clinically attractive than benzodiazepines [7]. However, adverse effects such as hallucinations and psychosis have been reported, particularly with zolpidem [8]. Increasing reports of bizarre and complex behavioral effects from z-drugs have prompted regulatory agencies to issue warnings and restrictions on prescribing, dispensing, and using z-drugs [9].

Barbiturates are classified as sedatives due to their central nervous system depressant and sleep-inducing effects. Primary therapeutic uses of barbiturates are as anesthetic and anticonvulsant medications. Barbiturate abuse — both prescription and illicit — peaked in the 1970s, but by the late 1980s, barbiturates had been largely replaced by benzodiazepines for treatment of anxiety and insomnia due to safety issues [10]. As the rate of barbiturate prescribing decreased dramatically, so did abuse of barbiturates [10]. Butalbital is a short-acting barbiturate that is combined with caffeine and aspirin (Fiorinal) or acetaminophen (Fioricet) and commonly prescribed for treatment of headaches. However, regular use of butalbital can lead to physical dependence and a withdrawal syndrome that starts with headaches, resulting in a vicious cycle of recurrent headaches (medication-rebound headaches) that are only relieved by frequent re-administration of butalbital. Most of those who abuse barbiturates will also have experience with other sedatives. It is rare for a patient to develop an addiction to barbiturates alone [10]. Abusers will take a variety of available sedatives to treat the unpleasant effects of illicit stimulants, reduce anxiety, or induce euphoric effects.

According to some surveys, up to 33 percent of elderly North American patients are prescribed either a benzodiazepine or z-drug for a sleep problem [11]. Patients who are elderly, women, or have poor perceived health status and poor actual physical health are associated with long-term use of sedatives, especially benzodiazepines [12]. Use of sedatives is strongly associated with an increased risk of falls and injury [13]. Older adults (over 64 years of age) are at risk of developing dependence on sedatives prescribed for insomnia or anxiety. Zolpidem and eszopiclone abuse is relatively rare when compared with benzodiazepine abuse, but patients with a history of a substance use disorder (SUD) or psychiatric comorbidity are at higher risk of abusing these medications [14]. The "high" from sedative medications is described as being very similar to alcohol intoxication. Tolerance, dependence, and withdrawal are all reported with sedatives, though these appear to be less severe and with lower incidence for z-drugs than for benzodiazepines or barbiturates [14]. Problems from misuse and abuse of sedatives have continued to grow with time. Substance abuse treatment admissions for benzodiazepine abuse nearly tripled from 22,400 admissions in 1998 to 60,200 in 2008 [15].

SELF-MEDICATION

Some patients take controlled substances that have been prescribed for specific conditions, such as sedatives for panic attack disorder, in order to obtain other benefits: to induce sleep, reduce anxiety from stressful life circumstances, elevate their mood when depressed, or provide additional energy. This behavior is a form of self-medication and has also been termed "chemical coping" [16]. Patients who engage in chemical coping may develop tolerance to the other effects of the sedative more rapidly than to the therapeutic effect for which it was prescribed, leading to dose escalation. Increases in emotional stress (disputes with family or friends, professional pressures, or financial worries) can heighten a patient's sensitivity to discomfort from anxiety symptoms, leading to increased consumption of controlled substance medications [17]. However, this is not the same as addiction or intentional malingering. Presentations of intentional malingering may include exaggerating symptoms of anxiety or insomnia; resisting access to outside medical records; deterioration or exacerbation of symptoms when medication dose is due to be reduced; a significant number of tests, consults, and

Table 1. Sedatives.

Generic name	Brand name	Slang name(s)	Typical oral dose (mg)	Typical dosing interval (hours)
Benzodiazepines				
Alprazolam	Xanax	Gold bars, schoolbus, X	1	6
Chlordiazepoxide	Librium	Lobbies	25	6
Clonazepam	Klonopin	Clozzies, k-pins, Klondike bars	2	8
Clorazepate	Tranxene	Tranx	7.5	8
Diazepam	Valium	Valley girls, Vs	10	6
Flunitrazepam	Rohypnol	Roofies, rope, Mexican Valium	1	
Flurazepam	Dalmane		15	12
Lorazepam	Ativan	Dots, lozzies, pam	2	8
Oxazepam	Serax		10	6
Temazepam	Restoril	Beans, temmies	15	6
Triazolam	Halcion		0.25	2
z-drugs				
Zolpidem	Ambien	Ambo, no-go pills, tic tacs, zombies	5-10	Once at bedtime
Zaleplon	Sonata		10	Once at bedtime
Eszopliclone	Lunesta	Clones, zops	1.5-3	Once at bedtime
Barbiturates				
Amobarbital	Amytal	Downers, blue heaven	100 (50-200)	6-8
Butalbital	Fiorinal, Fioricet	Barbs	100	4-6
Pentobarbital	Nembutal	Yellow jackets	100	3-4
Secobarbital	Seconal	Reds, red devils, pink ladies	100	3-4
Phenobarbital	Luminal	Goof balls, purple hearts	30-100	12

treatments have been performed with little success; noncompliance with diagnostic or treatment recommendations; or evidence from tests disputes information provided by the patient.

The patient in Case 1 has significantly escalated her dose of short-acting benzodiazepine (alprazolam) to self-medicate her symptoms of anxiety and depression. She does not abuse alcohol or illicit drugs and is not seeking euphoric effects. She has poor coping skills and minimal support, so she uses the available sedative to alter her mood. However, this has not significantly improved her depression or anxiety overall, and she has experienced some consequences of her sedative misuse (blackouts). A short-acting benzodiazepine is not an appropriate treatment of depression, especially when this patient is escalating the dose to attempt to achieve some symptom relief despite increased tolerance.

Chemical coping behavior is challenging for physicians to address. Somatization of psychological distress into physical symptoms is pervasive in medical practice [18], and the boundary between physical and mental distress is not clearly distinct for many patients. Use of prescribed sedatives becomes a reliable coping skill, but it is maladaptive. The challenge for the treating physician is to help patients identify the underlying (often subconscious) reasons for reliance on other inappropriate effects of the medication and then help the patient begin the process of developing new coping skills for dealing with symptoms of anxiety and depression. Utilization of specific antidepressant medications can be very effective as a way to shift the focus away from inappropriate use of sedatives toward treatment of the underlying condition. The selective serotonin reuptake inhibitors are safe, not prone to misuse, and can be accompanied by cognitive-behavioral therapy for long-term treatment of comorbid psychiatric diagnoses.

PRESCRIBING SAFETY

A thorough history is very important for safe prescribing of controlled substance medications. This includes past medications, vitamin/herbal supplements, substance abuse history, and any problems with medication management (running out early, going to the emergency department for medication refills, etc.). Screening instruments to assess risks related to sedative use are not readily available. Records from previous treatment providers and information from significant others help corroborate the patient's history. Some patient characteristics have been identified in research studies as risk factors for a higher likelihood of aberrant medication-taking behaviors (AMTB) due to addiction. A history of previous addiction, especially polysubstance use, is the strongest predictor of problems with management or abuse of controlled substance medications. Significant single substances are current tobacco smoking or a history of cocaine use [19]. Other characteristics indicating higher risk for medication abuse are younger age [20]; a history of childhood sexual abuse [19]; legal problems (especially charges for drug possession or driving under the influence)

[20]; a history of lost or stolen controlled substance prescriptions [21]; or obtaining controlled substance prescriptions from sources other than the primary prescriber, such as taking from a friend or family member, "doctor shopping," or buying on the street/black market [19]. A history of any of these indicators does not mean that the patient will definitely demonstrate serious AMTB or develop addiction, so they should not be used as a means to deny care to patients. The presence of risk factors such as these indicates a need for caution with the use of long-term controlled substance medications, including sedatives.

A Prescription Drug Monitoring Program (PDMP) is a statewide electronic database that collects information on selected medications dispensed in the state. The purpose of these programs is to promote the appropriate use of controlled medications for legitimate medical purposes while also deterring abuse and diversion [22]. Availability of PDMP data can provide clinicians with additional information to refute or corroborate what a patient tells a prescriber. This allows clinicians to make better decisions about prescribing for a given patient. Data from a PDMP helps determine the rate at which a patient is using a medication, based on dates of filling, refilling, or partial filling in relation to the original prescription date. Information from the PDMP can verify that patients are only obtaining controlled substance prescriptions from a single provider and a single pharmacy. Prescribers may also pick up on intentional use of multiple providers and/or multiple pharmacies by a patient, which is an AMTB that may indicate prescription drug abuse [17]. PDMP information is better used by the prescriber as a deterrent for the patient instead of as an attempt to "catch the patient in the act." As with other indicators described above, data from a PDMP should not be used as a means to deny care to high-risk patients but to raise awareness of a need for caution when prescribing. If a PDMP inquiry results in information that is concerning to the prescriber, this should be addressed with the patient. Informing the patient about the prescriber's concerns regarding specific AMTB and asking direct questions can help clarify any misunderstanding. This provides an opportunity to enhance patient-physician communication, and specific examples can be provided for expected and inappropriate behaviors. It is important to recognize limitations of PDMP data for clinical decision-making. Different states update data at different intervals, so the most recent prescription data may not be available. Only prescriptions filled at pharmacies within a specific state may be available in that state's PDMP. There is some reciprocity of data between different states that have an agreement for this purpose, but that may require the practitioner to register for access to a PDMP for each of several states. PDMP data does not cover illegally obtained prescription medications. For clinical decision-making, PDMP data is best used in combination with other medication monitoring strategies, such as those described below.

Sedative medication compliance can be monitored by having patients bring the original medication containers from the pharmacy to each visit so that the prescriber can count any unused medication to determine the rate at which the patient is taking the sedative [23]. These pill counts can also be performed between visits by calling the patient on short notice (up to 24 hours before) to bring the medication containers to the office. Urine drug testing (UDT) is another important component of medication monitoring. It verifies the presence of prescribed medications and identifies substances that should not be present in the patient's urine. This enhances the physician-patient relationship by providing documentation of adherence to the treatment plan. Problematic results should be discussed with the patient in a supportive fashion with the goal of encouraging appropriate patient behavior. Unfortunately, no individual immunoassay kit can recognize all benzodiazepines at clinically relevant concentrations [24]. Point-of-care immunoassays for benzodiazepines are usually optimized to detect alprazolam and diazepam, and they often yield false-negative results for benzodiazepines of other types, particularly lorazepam and clonazepam. If warranted by significant clinical concern, confirmatory testing for specific sedative metabolites can be requested from the testing laboratory.

Basic monitoring of patients being prescribed controlled substance medications requires some effort by the prescribing physician. This involves regular inquiries to a PDMP, only issuing prescriptions in person at scheduled office visits, pill counts, and random UDT [25] (see Table 2). A patient without significant risk factors may have only basic monitoring activities initially, such as one or two random UDT per year, a query to the PDMP once a year, and pill counts randomly at some office visits. Ongoing assessment and documentation of successfully met clinical goals (improved function, no AMTB) supports continuation of therapy. Failure to meet goals requires re-evaluation and a change in the treatment plan [26].

A thorough history and records from previous physicians can assist with determining in advance which patients are likely to need enhanced monitoring or whether basic monitoring activities are adequate when prescribing or continuing sedatives [17]. For example, a history of addiction and previous documentation of rapidly escalating medication doses are signs that should prompt closer monitoring of ongoing medication use. Such a patient may have UDT at nearly every visit initially, pill counts and UDT on short notice between visits, and queries to the PDMP every few weeks (if available and updated that frequently). The enhanced monitoring is to deter AMTB from occurring and assist the patient in achieving adequate medication management for better treatment outcomes. The clinician may utilize counseling strategies such as motivational interviewing to assist patients with medication management or may refer the patient to a behavioral therapist for additional assistance. As patients demonstrate appropriate ability to manage controlled substance med-

Table 2. Medication monitoring.

Monitoring activity	Rationale	Prescriber action	Minimal concern (basic monitoring)	Problems with management (enhanced monitoring)
Frequency of visits	Visit frequency may vary based on clinical condition, prescriber schedule, and patient compliance	Assess level of medication compliance and clinical outcomes	Every 1-3 months	Weekly or more frequent visits if necessary
Prescription drug monitoring program (PDMP)	Track all controlled substance prescriptions obtained by the patient	Request information from appropriate state agency (usually online)	At least once in 12 months	Every 2-4 weeks, depending on frequency at which data is updated by state PDMP
Verification of single prescriber	Limit sources for controlled substance prescriptions	Verify that patient has only one prescriber for all controlled substance prescriptions	Ask patient every few visits	Confirm at every visit and with PDMP
Frequency of prescriptions	Assess level of medication compliance demonstrated	Prescribe sufficient medication at each visit to last only until the next scheduled medication fill	30-day supply with sequential prescriptions until next appointment; maximum of 90 days	May provide only a few days of medication with sequential prescriptions to be filled between visits
Pill counts	Determine the rate at which the patient is using the medication	Have the patient bring in any remaining medication in the original containers from the pharmacy and count the pills	Randomly, every few visits for stable patients	At every visit and on short notice between visits
Urine drug testing	Confirm compliance with prescribed medications and abstinence from unauthorized substances	Test for the presence of illegal drugs or controlled substances not prescribed by the practitioner managing the patient's symptoms	Annually	As often as every visit, and may call in to give sample between scheduled visits
Collateral information	Corroborate patient history	Communicate with the patient's significant others after first obtaining permission	After initial evaluation	Ask family member or other to accompany patient to visits
Documentation	Clearly communicate ongoing plan of care with respect to prescribing	Document any concerns about aberrant medication-taking behavior, along with the plan for following up on the concerns	Every visit; affirm basic compliance	Every visit; more detail may be necessary about concerns and how addressed

ications, the enhanced monitoring can be gradually reduced over time to basic monitoring efforts.

Any patient may display AMTB at some point during treatment. For less serious problems, it is reasonable to initiate enhanced monitoring with more frequent visits and tighter limits on the amount of medication available at a time. For example, an isolated UDT positive for an illicit drug or unauthorized medication results in closer monitoring with more frequent UDT; recurrent positive results prompt referral to an addiction specialist for further evaluation and treatment. Repeated AMTB or patient refusal to adhere to all aspects of an addiction treatment program should result in loss of the privilege to receive controlled substance prescriptions but does not necessarily indicate that the patient should be discharged from treatment [25]. The physician may choose to continue to see the patient and provide other forms of treatment without controlled substance prescriptions [27].

CASE 1 RESOLUTION

The patient was identified as having chemical coping and was self-medicating her underlying depression symptoms with escalating doses of benzodiazepines due to her lack of appropriate coping skills. She was continued on clonazepam instead of alprazolam, which is shorter-acting and requires more frequent dosing. She was educated about taking doses on a set schedule every 6 hours to help avoid benzodiazepine withdrawal symptoms. She was instructed not to obtain benzodiazepines from any other prescribers, and her PMDP report was checked regularly to verify this. Her clonazepam tablets were counted at each visit, and she was seen weekly initially to evaluate her medication compliance. She was started on duloxetine (Cymbalta) as an antidepressant for treatment of depression and on trazodone (Desyrel) for insomnia, since these medications do not produce tolerance or physical dependence. She saw a therapist to work on coping skills enhancement and sleep hygiene techniques. After her symptoms of anxiety and depression began to improve, her clonazepam dose was gradually tapered down over several months.

CASE 2

A 23-year-old man presents for evaluation of benzodiazepine abuse. He has a long history of polysubstance addiction but has primarily been using alprazolam recently. He started using alprazolam 6 years ago when he got some tablets on the street from a buddy. In the past, he would binge-drink alcohol on weekends, he would smoke two bowls of cannabis daily, and he has snorted cocaine. He was able to stop most alcohol and drug use after completing a residential addiction treatment program 3 years ago, but he began abusing zolpidem (Ambien) after several months. After abusing larger doses of zolpidem, he switched back to abusing alprazolam. He escalated his alprazolam use to daily and would intranasally insufflate (snort) 2 mg tablets, usually five tablets per day. He tried to quit on his own several times without success because he would have tremors and diaphoresis when he stopped taking alprazolam abruptly. His work as a restaurant cook is occasionally impaired by his sedative use, and his mother is concerned about his addiction. He was stopped for driving while intoxicated and is currently on probation awaiting his court hearing. He wants to come off alprazolam now and is willing to go to counseling, but he is worried about having a seizure from sedative withdrawal.

INTOXICATION

The clinical features of acute sedative intoxication are similar to alcohol intoxication. Psychiatric manifestations include impaired attention, inappropriate behavior, labile mood, and impaired judgment. Physical signs include nystagmus, decreased reflexes, and unsteady gait. As the amount consumed increases, especially beyond the established tolerance of an individual, progressively more impairment occurs in judgment and brain function. Initial signs include slurred speech, followed by nystagmus, incoordination (especially in complex tasks such as driving), ataxia, and memory impairment (“blackout”) [28]. Severe overdose may lead to stupor, and high levels result in suppression of the autonomic respiratory drive and may result in coma or death from anoxic brain injury [29]. Long-term use of benzodiazepines can worsen underlying depression and anxiety [30]. A recent study showed that benzodiazepines accounted for nearly 30 percent of deaths from pharmaceutical agents, and 75 percent of overdose deaths were unintentional [31]. Another study of zolpidem misuse showed that hospital admission was common when zolpidem was ingested with other medications and resulted in intensive care unit admission in nearly half of cases for hemodynamic instability or prolonged altered mental status [32].

The patient in Case 2 has been abusing short-acting sedatives (zolpidem, which is a z-drug, and then alprazolam, a benzodiazepine) to experience intoxication with euphoric effects. However, this has caused impairment that has led to consequences at work and while driving. He also has a history of combining multiple drugs of abuse, which can cause serious consequences.

Initial management of intoxication and overdose involves general supportive care, as for any clinically significant intoxication, including maintenance of an adequate airway, ventilation, and cardiovascular function. Attention to airway patency and supportive management of ventilation and hemodynamics are usually sufficient [7]. Treatment of z-drug overdose is largely supportive, similar to benzodiazepine overdose, but with complete recovery expected within 6 hours due to the shorter duration of action of z-drugs. Following stabilization of respiratory and cardiac function, activated charcoal should be given [33]. A competitive benzodiazepine antagonist,

flumazenil (Romazicon), is available for the treatment of acute benzodiazepine intoxication and has been shown to reverse the sedative effects of all three z-drugs [34]. However, it may not completely reverse respiratory depression, and it can provoke withdrawal seizures in patients with benzodiazepine dependence [35]. Nausea and vomiting are its most common side effects. Flumazenil should be withheld in patients with current seizures or a history of seizures and in patients who have overdosed on other drugs that lower the seizure threshold. Flumazenil should not routinely be administered to comatose patients when the identity of ingested drug(s) is not certain. Flumazenil is short-acting and sedation may recur after an initial awakening, which can be treated by repeating doses at 20-minute intervals as needed. Repeat doses should be administered slowly in patients who are physically dependent on benzodiazepines or z-drugs.

WITHDRAWAL

Patients who chronically take sedative medications, whether prescribed by a physician or bought on the black market, are at risk for an acute withdrawal syndrome that is clinically indistinguishable from alcohol withdrawal. The severity of withdrawal is affected by concurrent medical illness [36]. Risk factors for severe withdrawal (delirium tremens) include larger amounts of sedatives taken chronically, longer time of use, older age, and comorbid medical or psychiatric problems. Few data are available about long-term physiological and psychological consequences of intermittent, high-dose use of sedatives in the setting of polysubstance use. Up to 20 percent of patients develop severe withdrawal if left untreated [37]. Recognition and effective treatment of withdrawal is important to prevent excess mortality due to complications. There is significant individual variability in the threshold at which a patient may develop withdrawal, so it is difficult to predict who will and who will not. The best predictor of whether a patient will develop acute withdrawal is a past history of acute withdrawal.

The clinical features of the acute withdrawal syndrome are identical for all sedatives, including alcohol (which may be considered a short-acting sedative), due to cross-tolerance. Abrupt reduction or cessation of sedative use results in a characteristic set of signs and symptoms, including tremor, anxiety, agitation, hyperreflexia, autonomic hyperactivity (e.g., elevated heart rate, blood pressure, temperature, and sweating), hallucinations, and seizures [38]. Withdrawal symptoms are the opposite of the symptoms of acute intoxication. The initial indication of withdrawal is an elevation of vital signs (heart rate, blood pressure, temperature). Tremors develop next, first a fine tremor of the hands and fasciculation of the tongue, sometimes followed by gross tremors of the extremities. Disorientation and mild hallucinations (often auditory, occasionally visual) may develop as the syndrome progresses, accompanied by diaphoresis. Seizures can be an early sign of withdrawal and may be the presenting symptom. The symptoms may appear as soon as 4 to 8 hours after the last dose, and withdrawal symptoms usually manifest within 48 hours, but for sedatives with long-acting metabolites the patient may not show signs of withdrawal for up to 7 to 10 days after stopping chronic use. Withdrawal symptomatology of z-drugs resembles that of other sedatives, including craving, insomnia, anxiety, tremor, palpitations, delirium, and, rarely, seizures and psychosis [39]. Withdrawal symptoms usually peak at around 5 days [40]. Some patients do not progress to severe withdrawal and the symptoms simply subside after a few days with or without treatment, but it is impossible to predict which patients will progress or not. The signs of severe withdrawal consist of worsening diaphoresis, nausea and vomiting (which may result in aspiration pneumonia), delirium with frank hallucinations, and rapid, severe fluctuation in vital signs [41]. Sudden changes in blood pressure and heart rate may result in complications such as myocardial infarction or a cerebrovascular event, and increased QT variability elevates the risk for serious cardiac arrhythmias [42]. Progression to severe withdrawal results in significant morbidity and even death [41], but adequate treatment early helps prevent progression of withdrawal.

The patient in Case 2 has developed tolerance and physical dependence on sedatives as a result of frequent use for euphoria. He experiences typical sedative withdrawal symptoms with cessation or reduction in dose. He is at risk to develop worsening symptoms of sedative withdrawal syndrome, including seizures and autonomic instability, which can lead to significant morbidity or even mortality. His sedative withdrawal syndrome will need to be treated to prevent these serious complications.

Chronic sedative use can result in a withdrawal syndrome that often requires detoxification with medication. Pharmacotherapy is indicated for management of moderate to severe withdrawal. However, there is little consistency in treatment of withdrawal, and there are no standard protocols for withdrawal management in widespread use [43]. Both benzodiazepines and barbiturates are effectively used to treat withdrawal and have been studied in clinical trials [44]. Barbiturates have been used successfully to treat acute sedative withdrawal syndrome in a variety of clinical settings, and phenobarbital (Luminal) has been used most commonly. Benzodiazepines have largely replaced barbiturates for pharmacologic prevention and management of sedative withdrawal syndrome, and the choice of benzodiazepine depends on characteristics such as duration of action, need for metabolism, and speed of onset of effects. However, for patients who have been abusing benzodiazepines, a different type of sedative may be appropriate to use for treatment of withdrawal symptoms, such as phenobarbital. Non-benzodiazepine anticonvulsants such as carbamazepine and gabapentin have been used for treatment of mild to moderate alcohol withdrawal and may be useful for treatment of withdrawal from other sedatives [45].

Stable patients on moderate doses of a sedative may be tapered off in the outpatient setting. This may be accomplished by gradually reducing the dose of the sedative over several weeks. It is usually better to reduce the dose rather than the dosing interval in order to avoid development of sedative withdrawal symptoms between doses. For patients coming off short-acting sedatives, it may be better to substitute a long-acting sedative. Clonazepam is a long-acting benzodiazepine with generally less euphoria than other benzodiazepines such as diazepam or chlordiazepoxide (Librium), so it is more suitable for detoxification. Phenobarbital is a long-acting barbiturate that may be preferable to other sedatives for treatment of acute sedative withdrawal syndrome [46]. It has a long half-life of up to 100 hours [47], dosing is very flexible (it can be given orally as tablets or elixir, or administered parenterally), it is inexpensive, and there is almost no street market for it, in contrast to the benzodiazepines.

Acute withdrawal is most safely managed in an inpatient setting if the patient has been using high doses of sedatives, has a history of seizures or delirium tremens, or has unstable comorbid medical or psychiatric problems [48]. This allows for close medical monitoring during treatment of sedative withdrawal to prevent complications from progression to severe withdrawal, which can be life-threatening.

A prolonged benzodiazepine withdrawal syndrome, or symptom rebound, may be seen following long-term use of benzodiazepines [28]. This can manifest after a relatively short tapering off of the benzodiazepine. Symptoms of insomnia and anxiety may last for several months. Although not life-threatening, this prolonged abstinence syndrome may be sufficiently uncomfortable that it may trigger a relapse to sedative use or abuse. To avoid this, it may be useful to taper the original benzodiazepine — or a long-acting substitute such as clonazepam or phenobarbital — over an extended time period of 2 to 3 months [49].

TREATMENT OF SEDATIVE ADDICTION

Acute and long-term treatment is necessary once the diagnosis of SUD is made [50]. Recovery from SUD is possible, and those who are treated have less disability than those who remain untreated [51]. Patients identified with SUD should be provided with information linking them to local community addiction treatment resources. In the United States, physicians certified in treatment of addictive disorders can be found through the American Society of Addiction Medicine (www.asam.org) or the American Academy of Addiction Psychiatry (www.aaap.org). At times, it may be more expedient and cost effective to refer the patient to a non-physician counselor [52], which can be found through the National Association for Alcohol and Drug Abuse Counselors (www.naadac.org). There are several types of formal counseling available for treatment of problems due to abuse of sedatives. Motivational interviewing is a counseling style that seeks to motivate the patient to reduce or stop drug use and/or seek further treatment. Cognitive-behavioral treatment helps patients identify life stressors, high-risk situations for drug use, and coping skills deficits, then uses modeling and rehearsal to address these. Relapse prevention helps identify triggers, practices avoiding them, and emphasizes responsibility for recovery.

The patient in Case 2 clearly has sedative addiction and would benefit from specific addiction treatment. Addressing intoxication or withdrawal is only the initial step in overall treatment of his addiction. Detoxification is not sufficient treatment in itself, and long-term addiction treatment can lead to recovery with less disability [51]. Referral for counseling in group and/or individual format should be offered to the patient. This can help prevent worsening medical and psychiatric consequences of sedative addiction.

CASE 2 RESOLUTION

The patient was started on phenobarbital to transition from the short-acting benzodiazepine he has been abusing to a long-acting cross-tolerant medication for tapering off sedatives. This was accomplished as an outpatient because the patient had good support at home from his mother and was able to come to the clinic for frequent visits to monitor his response to the medication. His dose was adjusted to prevent withdrawal symptoms and avoid over sedation. He was referred for individual drug counseling with a therapist. He had regular UDT for illicit and unauthorized drugs. He was able to stop using alprazolam and taper completely off phenobarbital over several weeks. After stopping all sedative medications, he remained abstinent by continuing counseling sessions and developing a personal recovery support system.

CONCLUSIONS

There are many different types of sedatives, and they are widely prescribed for insomnia and anxiety. Benzodiazepines are very popular, especially alprazolam and diazepam. Non-benzodiazepine z-drugs are also very popular and prone to many of the same problems as benzodiazepines. Barbiturates and older sedatives are much less commonly prescribed, although butalbital is a cause of medication-rebound headaches. Patients may misuse sedatives to self-medicate symptoms of underlying depression or anxiety, a condition sometimes known as chemical coping. Sedatives may be abused recreationally for euphoria, either obtained from prescribers under false pretenses directly for this or diverted to the black market and sold on the street. The number of admissions to addiction treatment programs for sedative abuse has continued to grow. To help prevent abuse and diversion of sedatives, prescribers should use appropriate precautions, similar to those used when prescribing other controlled

substances such as opioids. This includes obtaining previous medical records, utilizing the state PDMP, performing pill counts and UDT, and promptly addressing any AMTB with the patient.

Misuse or abuse of sedatives may lead to intoxication or a withdrawal syndrome, either of which may be fatal. Fortunately, overdose with benzodiazepines and z-drugs responds to an antagonist, flumazenil, although it has its limitations and potential adverse effects. Sedative withdrawal syndrome can be avoided by slowly tapering down the dose of the sedative over several weeks. More serious withdrawal is treated by substitution with a long-acting sedative and requires close medical supervision in the outpatient or inpatient setting. After treatment of these consequences, the SUD should be addressed with long-term treatment that involves individual and/or group counseling with the help of an addiction treatment professional.

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