A Review of Alprazolam Use, Misuse, and Withdrawal

Nassima Ait-Daoud, MD, Allan Scott Hamby, MD, Sana Sharma, MD, and Derek Blevins, MD

Alprazolam is one of the most widely prescribed benzodiazepines for the treatment of generalized anxiety disorder and panic disorder. Its clinical use has been a point of contention as most addiction specialists consider it to be highly addictive, given its unique psychodynamic properties which limit its clinical usefulness, whereas many primary care physicians continue to prescribe it for longer periods than recommended. Clinical research data has not fully shed light on its ''abuse liability,'' yet it is one of the most frequently prescribed benzodiazepines. ''Abuse liability'' is the degree to which a psychoactive drug has properties that facilitate people misusing it, or becoming addicted to it, and is commonly used in the literature. We have replaced it in our manuscript with ''misuse liability'' as it reflects a more updated terminology consistent with the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). In this paper, we have reviewed alprazolam's indications for use, its effect on pregnant women, misuse liability, withdrawal syndrome, pharmacodynamic properties, and suggest better clinical prescription practice of alprazolam by presenting an indepth theory of its clinical effects with use and withdrawal.

Key Words: alprazolam, benzodiazepines, generalized anxiety disorder, misuse, panic disorder, withdrawal

(*J Addict Med* 2018;12: 4–10)

Alprazolam is not only the most commonly prescribed benzodiazepine, but it is the most commonly prescribed psychotropic medication in the United States, accounting for more than 48 million prescriptions dispensed in 2013 (Grohol, 2016). This persists despite the fact that many prescribers consider alprazolam to have high misuse liability and it is shown to result in a more severe withdrawal syndrome than other benzodiazepines, even when tapered according to manufacturer guidelines (Browne and Hauge, 1986; Kantor, 1986). Based on national emergency department (ED) visit data, alprazolam is the second most common prescription medication and the most common benzodiazepine to be involved in ED visits related to drug misuse (SAMHSA, 2013).

Benzodiazepines are implicated in approximately one-third of intentional overdoses or suicide attempts (Henderson et al., 1993). A database review of poisoning admissions to a regional toxicology service revealed that when alprazolam was involved, the median length of stay (LOS) was 19 hours, which was 1.27 (95% confidence interval [CI] 1.04, 1.54) times longer compared with other benzodiazepines, and patients were 2.06 (95% CI 1.27, 3.33) times more likely to be admitted to the intensive care unit (ICU) compared with other benzodiazepines after multivariate analysis adjusting for age, dose, sex, time to ingestion, and co-ingested drugs (Isbister et al., 2004). In a longitudinal cohort study between July 1, 2011, and June 30, 2012, more than half of the patients who visited hospital and ''community practice-based research network'' received benzodiazepine prescriptions at least once from their primary care physician (PCP). Those clinicians were found to prescribe benzodiazepines disproportionately to patients with at least some known risk factors for benzodiazepine-related adverse events including increased age, pulmonary diseases, and other substance use disorders (Kroll et al., 2016).

There are significant discrepancies between prescribing habits and risk associated with the use of benzodiazepines, including alprazolam, largely due to the lack of important data informing clinicians on best clinical practice. While more recent research studies involving benzodiazepines are scant, the subject of alprazolam misuse continues to be a reality with which many providers struggle and should continue to be addressed. We have performed an indepth review of the alprazolam literature, summarizing older and newer publications, in an attempt to provide a better understanding of how alprazolam's unique pharmacokinetic and pharmacodynamic properties affect its misuse liability and offer some prescription guidelines for its safe and effective use.

INDICATIONS FOR USE AND EFFICACY

Alprazolam is a high-potency triazolobenzodiazepine that is US Food and Drug Administration (FDA)-approved for the treatment of anxiety and panic disorders. Alprazolam is biotransformed by hepatic microsomal oxidation, yielding 4 and α-hydroxyalprazolam as its principal metabolites, and is metabolized by cytochrome P450 (CYP) 3A4 (Greenblatt and Wright, 1993).

The US FDA's approval for alprazolam came after 2 large, randomized, clinical trials that demonstrated short-term efficacy and clinically acceptable tolerability versus placebo (Ballenger et al., 1988; Klerman, 1988). A plasma

From the University of Virginia, Department of Psychiatry and Neurobehavioral Sciences. Charlottesville, VA (NA-D, SS, DB); Sentara RMH Medical Center: 2010 Health Campus Drive, Harrisonburg, VA (ASH).
Received for publication March 29, 2017; accepted July 2, 2017.
The authors report no conflicts of interest.
Send correspondence to Nassima Ait-Daoud, MD, Associate Professor, University of Virginia, Department of Psychiatry and Neurobehavioral Sciences, P.O. Box 800623, Charlottesville, VA 22908. E-mail: nat7b@virginia.edu.

ISSN: 1932-0620/17/1201-0004
DOI: 10.1097/ADM.0000000000000350

concentration range between 20 and 40 ng/mL has been suggested for targeting symptoms of panic disorder, with higher concentrations being associated with more significant central nervous system depressant effects. The side effects of alprazolam tablets are likely to be an extension of its pharmacological activity, and most commonly include drowsiness, dizziness, fatigue, dysarthria, headache, memory impairment, and depression.

In a review of its efficacy as monotherapy for the treatment of anxiety, panic disorder, and depression, Jonas and Cohon (1993) reviewed 84 studies of alprazolam versus active-drug comparators and/or placebo. They found that alprazolam was superior to placebo and as effective or superior to all comparator benzodiazepines, including diazepam, lorazepam, and bromazepam; all comparator antidepressants, including amitriptyline, imipramine, and dothiepin (or dosulepin, a tricyclic antidepressant not approved for use in the United States); and buspirone for the treatment of anxiety disorder, as measured by reductions in the Hamilton Rating Scale for Anxiety (HAM-A). The review found that the onset of the anxiolytic effect was significantly more rapid for alprazolam compared with amitriptyline, and its antipanic effect was significantly more rapid compared with propranolol and imipramine. However, a 2011 meta-analysis of all single or double-blind, randomized controlled trials comparing alprazolam with other benzodiazepines in the treatment of panic disorder found no significant differences on any of the outcomes of clinical efficacy, including mean panic attack frequency, improvement in HAM-A score, and proportion of patients free of panic attacks at the final evaluation (Moylan et al., 2011). Alprazolam is relatively more toxic than other benzodiazepines in overdose. Alprazolam has been consistently found to approximate the magnitude of anxiolytic effect of other comparable benzodiazepines.

Alprazolam has also been used off-label for the treatment of depression, but its antidepressant effects have not been systematically evaluated. In a review of 25 studies (Jonas and Cohon, 1993) (n = 2643), alprazolam was found to be superior to placebo, and as effective as all comparator antidepressants, including amitriptyline, clomipramine, desipramine, dothiepin, doxepin, and imipramine, for the treatment of ''neurotic'' or moderate depression, whereas the comparator antidepressants were perhaps superior to alprazolam for the treatment of severe depression. The diagnosis of ''neurotic depression'' was mostly reflecting depressive symptoms associated with major personality disorders. According to the review, data from several studies showed the onset of antidepressant effect was significantly more rapid for alprazolam compared with the antidepressants, and alprazolam was just as well-tolerated as all comparator medications. A Cochrane review of alprazolam's efficacy as antidepressant monotherapy evaluated 21 more recent randomized controlled trials and found that alprazolam was superior to placebo, and as effective as the tricyclic antidepressants, including amitriptyline, desipramine, dothiepin, doxepin, and imipramine, and the heterocyclic antidepressant mianserin, for the treatment of depression in adults, as measured by reductions in the Hamilton Rating Scale for Depression (HAM-D) (van Marwijk et al., 2012). However, the authors concluded that the studies included in the review were heterogeneous, of poor quality, and only addressed short-term effects, thus limiting the significance of the findings. Additionally, it was not clear if the clinical effect of alprazolam was due to a unique antidepressant effect or rather a nonspecific effect on co-occurring anxiety and sleep-related issues. The authors also questioned the funding sources of the trials and the possibility of interpretation bias favoring alprazolam, as no other trial involving other benzodiazepines has been conducted for this indication.

It is also worth noting that the number of clinical trials involving alprazolam significantly decreased circa the advent of newer antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), and that there are no clinical trials directly comparing alprazolam or any other benzodiazepines with SSRIs or other newer antidepressants as monotherapy for anxiety disorder, panic disorder, or depression. However, while the available data show that alprazolam monotherapy is as effective as other benzodiazepines for the treatment of anxiety and panic disorders, this must be considered along with its propensity for tolerance, dependence, and rebound anxiety.

ALPRAZOLAM AND PREGNANCY

The US FDA has identified alprazolam and other benzodiazepines as pregnancy category D, which indicates prior evidence of human fetal risk. Twenty-one to 33% of pregnant females are estimated to receive psychotropic drugs (Levenson, 2011), and often these medications are prescribed to treat psychiatric symptoms that predate the pregnancy. Despite the risks, benzodiazepines are often used during pregnancy to manage symptoms of anxiety. In some cases, they are continued throughout the pregnancy, even when they are no longer clinically indicated, because the pregnant mother is physically dependent and discontinuation could harm the fetus due to increased risk of withdrawal symptoms, including seizures. Data from a systematic review that included 9 observational studies with more than one million subjects suggested that benzodiazepines are not associated with an increased risk of teratogenicity (NICE, 2014). However, dysmorphism and mental retardation resembling those observed with fetal alcohol syndrome have been reported in 8 Swedish children born of mothers who had taken high doses of benzodiazepines regularly throughout pregnancy (Laegreid et al., 1989). Other retrospective studies also suggest that benzodiazepines or hypnotic benzodiazepine receptor agonists could be associated with congenital malformations (Altshuler and Cohen, 1997; ACOG, 2007). To the extent that benzodiazepines are associated with teratogenic effects, many experts consider the absolute increase to be small (Dolovich et al., 1998; Yonkers et al., 2004).

Alprazolam and its 2 hydroxylated metabolites are known to cross the placenta. Retrospective studies evaluating pregnancy outcomes of women exposed to alprazolam during the first trimester of pregnancy found conflicting results of congenital anomalies (Iqbal et al., 2002). Positive studies reported the occurrence of cleft lip, inguinal hernia, hypospadias, cryptorchidism, tracheoesophageal fistula, microcephaly, strabismus, congenital hip dislocation, and neonatal

withdrawal syndrome, although no clear relationship was found between the use of alprazolam and the congenital malformations (Iqbal et al., 2002).

Alprazolam is also excreted into breast milk in low concentrations. There are few case reports of alprazolam causing neonatal withdrawal syndrome and mild drowsiness in nursing infants (Iqbal et al., 2002).

Given the significant concerns of potential risk, but conflicting reports of causation of teratogenic effects, a careful risk-benefit analysis and informed consent is critical when considering prescribing alprazolam for pregnant or breastfeeding women.

MISUSE LIABILITY

All experiments using double-blind, placebo-controlled human laboratory designs have demonstrated that benzodiazepines, as a class, produce reinforcing effects indicating misuse liability in subjects with histories of drug misuse (Griffiths and Wolf, 1990). Head-to-head benzodiazepine comparison studies in general have been scant. Two clinical studies of participants with benzodiazepine dependence revealed a significant preference for alprazolam over diazepam in equipotent doses (Schmauss et al., 1988, 1989). However, in another study of recreational drug users without physical dependence, alprazolam was found to have less misuse liability than diazepam (Orzack et al., 1988). Most prescribers with experience in addiction medicine consider alprazolam to have high misuse liability, especially when prescribed to individuals with a history of some type of substance use disorder (Griffiths and Wolf, 1990). Another study suggested that individuals with a history of alcohol or opiate use prefer alprazolam to other benzodiazepines (eg, chlordiazepoxide and oxazepam) as they found it to be more rewarding (Ciraulo et al., 1997; Iguchi et al., 1989; Wolf et al., 1989). Similarly, in a small double-blind study of 14 inpatients with a history of benzodiazepine dependence who were undergoing benzodiazepine withdrawal, alprazolam was preferred to equipotent doses of diazepam in a drug choice test (Apelt et al., 1990). Not surprisingly, the national ED visit data and national prescription data show that alprazolam is related to more ED visits related to drug misuse per prescription (1 in 311) than the next 3 most commonly prescribed benzodiazepines—lorazepam (1 in 540), diazepam (1 in 517), and clonazepam (1 in 321) (SAMHSA, 2013; Grohol, 2016). CDC prescription death rate data reveal that between 2003 and 2009, alprazolam had the highest death rate increase of all benzodiazepines and second highest overall at 234%, compared with 168% for benzodiazepines as a class (CDC, 2011).

Alprazolam's misuse potential stems from its unique pharmacokinetic properties of rapid absorption, low lipophilicity, and short half-life ($t_{1/2}$), and pharmacodynamic properties of high potency and more severe withdrawal symptoms occurring after a shorter period of use. Compared with diazepam, alprazolam is less lipophilic, thus having a smaller volume of distribution, and is less protein-bound at 68%, compared with 98% for diazepam, meaning its faster metabolism and shorter duration of action would increase its abuse liability more so than that of diazepam. The half-life of diazepam in healthy young volunteers is 22 to 72 hours and is oxidatively metabolized to desmethyldiazepam ($t_{1/2} = 30–300$ hours). The half-life of alprazolam is much shorter (8–16 hours), with no accumulation of oxidative metabolites. Diazepam and its metabolites accumulate in the body, followed by a slow washout once the drug is discontinued, thus triggering fewer withdrawal symptoms than the more rapidly eliminated alprazolam. Additionally, alprazolam—a triazolobenzodiazepine—is a more potent benzodiazepine than diazepam, with a 1 mg alprazolam being equipotent to 10 mg of diazepam (NICE, 2014). There is no clear evidence suggesting the increased potency of the triazole moiety is increasing its potential for dependence or addiction, though it is hypothesized that the triazole moiety may have unique receptor-binding effects which are not fully known (Juergens, 1991). The triazole ring may also play a role in the metabolism of alprazolam. Compounds with a triazole ring or a fused imidazole ring, such as midazolam, are metabolized rapidly by α-hydroxylation of the methyl substituent on the triazole or imidazole ring. The resulting active α-hydroxylated metabolite is quickly inactivated by glucuronidation, making the drug short-acting.

In addition to its pharmacological properties which may contribute to its increased misuse potential, alprazolam uniquely affects the dopaminergic function in the striatum similarly to stimulants. Administration of alprazolam, and not lorazepam, has been found to elicit a significant increase in extracellular dopamine concentrations in the striatum and a marked trend towards increased levels of serotonin, which induced behavioral stimulatory effects on animals (Bentue-Ferrer et al., 2001). The striatum is a heterogeneous structure connected to dopaminergic reward circuitry, receiving input from the prefrontal cortex and ventral tegmental area to guide behavioral output, including motor planning, decision-making, motivation, and reward. Most drugs involved in misuse or addiction consistently lead to dopamine release in the striatum (Di Chiara and Imperato, 1988; White and Kalivas, 1998; Willuhn et al., 2010; Vander Weele et al., 2014).

Most studies conducted to assess benzodiazepines misuse liability in head-to-head comparisons are more than 20 years old. With the approval of the long-acting formulation, some would argue that the risks, and several of alprazolam unfavorable pharmacokinetic properties, including rapid absorption and short half-life, would be mitigated when alprazolam is prescribed in its extended-release formulation (alprazolam-XR).

In a study of 14 outpatients with a history of sedative misuse, alprazolam immediate-release (IR) at 2 and 1 mg doses increased all 6 measures of positive drug effects, including ratings of "liking," "good effects," and "strength." Alprazolam-XR at a dose of 2 mg per day did not increase any of the same 6 measures of positive drug effects, but 3 mg per day increased 3 of the 6 measures, mainly "liking" and "good effects." Participants were willing to pay more money to retake alprazolam compared with placebo for both immediate and extended-release formulations (Mumford et al., 1995). While the data for this small human laboratory study may seem to suggest that the extended-release alprazolam may have less misuse potential, there is a clear dose effect with the extended-release form, with the higher dose being associated

with more positive drug effects. The recommended dose for the extended-release formulation ranges between 3 and 6 mg daily, and therefore higher doses within the recommended range could be associated with a similar degree of misuse potential as the IR formulation.

THE TOLERANCE PHENOMENON

Long-term use of benzodiazepine in general is controversial and not recommended, although commonly practiced. Interestingly, tolerance was found to develop relatively quickly for the hypnotic, sedative, and anticonvulsant actions of all benzodiazepines, whereas results on tolerance to anxiolytic and amnesic effects have not been consistent across studies or molecules tested (Lucki and Rickels, 1986; Lucki et al., 1986; Curran et al., 1994). It is important to note that physical dependence, usually defined by withdrawal symptoms including seizures, does not require the presence of clinical tolerance, and conversely tolerance may develop without any signs of physical dependence. Furthermore, the degree of cognitive recovery that may take place after a benzodiazepine taper is unclear, with compelling evidence not supporting full restitution of cognitive function, at least in the first 6 months after cessation, and suggestion that there may be some permanent deficits in comparison to controls (Barker et al., 2004). In a controlled longitudinal study of alprazolam for the treatment of panic disorder with agoraphobia, alprazolam produced pronounced impairments on a word recall task at baseline and at the 24-week medication-free follow-up (Curran et al., 1994).

In another study of patients with panic disorder, neither anxiolytic tolerance nor daily dose increase was observed after 8 weeks of alprazolam treatment, with continued efficacy at 6 months (Schweizer et al., 1993). There is a subpopulation of patients exposed to benzodiazepines that is more likely to escalate their dose, mainly those with coexisting drug or alcohol use problem (Griffiths and Wolf, 1990; NICE, 2014). Most would agree that tolerance is a multifactorial process that occurs at different rates for different patients, and also depends on the profile of the benzodiazepine used. In general, available data have been inconsistent with large variance between studies highlighting the need of well-designed long-term clinical trials addressing the question of tolerance with all benzodiazepines including alprazolam.

ALPRAZOLAM WITHDRAWAL SYNDROME

Alprazolam and alprazolam-XR carry the same general risk of withdrawal as other benzodiazepines. The manufacturer recommends a taper not to exceed 0.5 mg every 3 days (Kantor, 1986). Alprazolam use for merely 1 week produces discontinuation symptoms in mice (Galpern et al., 1991), and the withdrawal syndrome associated with its discontinuation is generally regarded as being more severe than other benzodiazepine withdrawal syndromes, even when alprazolam is tapered according to manufacturer guidelines (Browne and Hauge, 1986; Kantor, 1986). Specifically, alprazolam withdrawal syndrome has been described as involving a more complicated and, in some aspects, unique rebound anxiety compared with other benzodiazepine withdrawal syndromes (Browne and Hauge, 1986). One study reported that of 17 patients with panic disorder treated with alprazolam, 15 patients had recurrence or an increase in their panic attacks, and 9 had significant new somatic symptoms, such as malaise, weakness, insomnia, tachycardia, and dizziness, after alprazolam discontinuation, despite a taper over 4 weeks (Fyer et al., 1987). Another study reported that of 126 patients with panic disorder treated with alprazolam, 27% of patients had rebound anxiety that was more severe than pretreatment anxiety, and 35% of patients had new somatic symptoms after alprazolam discontinuation, despite a taper over 4 weeks (Pecknold et al., 1988). In a case series of 8 patients with combat-induced post-traumatic stress disorder (PTSD) treated with alprazolam at an average dose of 4.9 mg per day, all 8 patients developed worsening anxiety, sleep disturbance, and nightmares, 7 patients had irritability and hyperalertness, 6 patients had rage reactions and homicidal ideation, and 4 patients developed dissociative reactions and suicidal ideation upon alprazolam discontinuation, despite a taper over an average of 8.4 weeks (Risse et al., 1990). Another study demonstrated that alprazolam withdrawal causes more frequent and severe sleep disturbances compared with diazepam withdrawal (Kales et al., 1988).

Alprazolam withdrawal syndrome may also feature unique clinical symptoms compared with other benzodiazepine withdrawal syndromes. There are several case reports of delirium and psychosis caused by alprazolam withdrawal, whereas there are scant reports of these symptoms in cases of other benzodiazepine withdrawal (Zipursky et al., 1985; Freiberger and Marsicano, 1991; Zalsman et al., 1997; McKenzie et al., 2014). There are several case reports of hyperadrenergic states caused by alprazolam withdrawal (Páll et al., 2014), with the most impressive example describing a pseudo-pheochromocytoma, characterized by intermittent episodes of hypertensive crisis with sinus tachycardia, some so severe as to require ICU admission. Interestingly, despite ICU care and administration of beta-blockers and alpha-blockers, the pseudo-pheochromocytoma was only successfully treated by alprazolam re-instatement (Orzack et al., 1988).

The use of other benzodiazepines in treating alprazolam withdrawal is quite common, yet not fully investigated. Often switching to a long-acting benzodiazepine with inherent accumulation of metabolites, followed by a gradual dose taper, are effective strategies resulting in a safe and smoother detoxification for most cases. However, interestingly, both chlordiazepoxide and diazepam were found to be ineffective in preventing alprazolam withdrawal symptoms in 2 separate cases (Schweizer et al., 1993; Sachdev et al., 2014). Lorazepam was also found to be ineffective in controlling alprazalom-induced withdrawal symptoms in a critically ill patient who was admitted to the ICU (Risse et al., 1990). This lack of response has been consistent when switching from a triazolobenzodiazepines, such as alprazolam and triazolam, to a benzodiazepine with no triazole moiety. The triazole ring may have a unique binding affinity for a subgroup of benzodiazepine receptors that are not generally affected by other benzodiazepines (Albeck, 1987), making substituting alprazolam with another benzodiazepine less effective in preventing rebound anxiety and withdrawal symptoms. There are

published data on open-label clinical observations of 37 alprazolam-dependent patients who were successfully tapered from alprazolam using clonazepam substitution, with only 2 patients experiencing rebound panic symptoms, and no patients experiencing any other withdrawal symptoms (Patterson, 1990). Clonazepam is usually chosen because it has an intermediate to long half-life, ranging from 17 to 60 hours, and is associated with less rebound anxiety and withdrawal symptoms in comparison with shorter-acting agents. One should be mindful that longer-acting drugs have shorter durations of action when given acutely because of their pharmacokinetic properties, requiring a few days to a week to reach steady state. It is therefore recommended that for the first week, the substitution should be given on a twice or 3 times per day schedule.

Perhaps even more interestingly, there are reports of successful treatment of the alprazolam withdrawal syndrome using carbamazepine (Klein et al., 1986) and clonidine, neither of which has appreciable affinity for benzodiazepine receptors (Vinogradov et al., 1986; Fyer et al., 1988). The mechanism of action of carbamazepine remains unknown, but there is limited evidence suggesting that carbamazepine can increase gamma-aminobutyric acid (GABA) concentrations, possibly by decreasing turnover and inhibiting sodium channel-mediated neuroexcitation (Galpern et al., 1991). Carbamazepine is also known to enhance catecholamine function and therefore may improve symptoms of sleep disturbance, anxiety, and mood instability, which are common in withdrawal. This explains its positive effects in general for the treatment of benzodiazepine withdrawal syndrome. It is also consistent with open-label reports and a double-blind study supporting the use of carbamazepine in benzodiazepine withdrawal (Björkqvist et al., 1976). In contrast to other benzodiazepines, alprazolam activates alpha-2 adrenoceptors, which could account for its reported enhanced effectiveness in the treatment of panic disorder, but also the hyperadrenergic state seen with its discontinuation (Eriksson et al., 1986). Rebound anxiety is common and is often severe with alprazolam discontinuation because of its short half-life and the unique alpha-2 adrenergic effect. Both carbamazepine and clonidine act at the alpha-2 adrenoceptors level and could counteract the hyperadrenergic state that has been reported during discontinuation of alprazolam. Both drugs were also found to act synergistically via carbamazepine induced supersensitivity of the alpha-2-adrenergic receptors through which clonidine exerts its primary effect (Dilsaver et al., 1993), although, to our knowledge, this combination has not been used to treat the alprazolam withdrawal syndrome. Conversely, there are reports of withdrawal from carbamazepine and clonidine with symptoms similar to those seen in alprazolam withdrawal, including psychosis (Adler et al., 1982; Heh et al., 1988) and hyperadrenergic states (Tollefson, 1981). Thus, alprazolam likely has unique pharmacodynamic properties that contribute to its distinctive withdrawal syndrome, would theoretically prohibit complete cross-tolerance between alprazolam and other benzodiazepines, and may be related to the putative pharmacodynamic properties of carbamazepine and clonidine. Carbamazepine is metabolized by CYP3A4, and interactions with other drugs that induce, inhibit, or compete for CYP3A4 are relatively common, which may limit its use. Clonidine acts exclusively at the alpha-2 adrenoceptors levels and lacks carbamazepine's GABAergic function and mood stabilization, thus leaving patients to experience all the other withdrawal symptoms if used alone for detoxification.

There are also encouraging case reports and case series with the use of other antiseizure medications to help alleviate symptoms of benzodiazepine withdrawal. There are 3 case reports suggesting that valproate may be effective for the treatment of sedative-hypnotic withdrawal, but a double-blind, placebo-controlled study failed to replicate the results (Rickels et al., 1999). When gabapentin, an antiseizure medication with high affinity for voltage-gated calcium channels was added to a structured withdrawal regimen in patients with benzodiazepines use disorder for rapid inpatient withdrawal (less than a week); patients experienced minimal discomfort and the added benefit of reduced cravings for benzodiazepines (Penders, 2015).

CONCLUSIONS

Alprazolam is the most widely prescribed and misused benzodiazepine in the United States. It can be used safely and effectively when prescribed appropriately, after thoroughly evaluating the risks and benefits of treatment. Side effects are common, but often downplayed by patients, given its rapid onset of therapeutic action and unique reinforcing properties. Common complaints reported with varying frequency by patients treated with alprazolam include sedation, fatigue, ataxia, amnesia, slurred speech, poor concentration, hypersensitivity, and irritability.

All benzodiazepines carry a risk of misuse, diversion, tolerance, and physical dependence. Misuse and diversion are more frequently seen in patients with a personal or family history of alcohol or drug misuse (Ciraulo et al., 1997). Withdrawal symptoms associated with alprazolam discontinuation seem to be more severe than with other benzodiazepines probably due to its shorter half-life, high potency causing severe rebound anxiety, and it is affinity to the alpha-2 adreno-receptors. Some of the risks listed above could be mitigated with the use of alprazolam-XR, although little is known about the long-acting formulation, except for one small human laboratory study indicating that lower doses were not as reinforcing as the IR formulation.

Alprazolam has been reported to cause withdrawal and sedation in the newborn and should be avoided during pregnancy and lactation. As a general rule, exposure to any type of benzodiazepine during the first trimester should be avoided.

Alprazolam is significantly more toxic than other benzodiazepines in cases of overdoses and should be avoided in patients at increased risk of suicide, or who are using alcohol, opioids, or other sedating drugs. Generally, SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs) are considered first-line pharmacological treatment for anxiety disorders (Baldwin and Polkinghorn, 2005; Bandelow et al., 2008), but it usually takes few weeks to reach therapeutic effects, and therefore benzodiazepine use may have a role in alleviating acute symptoms of anxiety and distress early in treatment (Nutt, 2005). Alprazolam should be prescribed primarily in its extended-release formulation for

a short duration to minimize misuse liability and only to those with no prior substance use history. Prescribers should take measures to ensure patients taking alprazolam are not co-ingesting other CYP3A4 substrates, especially opioids, to minimize morbidity and mortality associated with co-ingested substances. The use of benzodiazepines with opioids doubles the risk of respiratory depression and death, and should be avoided. In the rare instance that patients require both an opioid and benzodiazepine, or during the tapering phase, patients should be alerted to the risk of death and offered a prescription of the opioid antagonist naloxone. Grapefruit and grapefruit juice should also be avoided, as they contain furanocoumarins that inhibit CYP3A4 and therefore cause blood levels of alprazolam to increase. This may be accomplished by fostering open communication about diet and substance use with patients, regularly checking prescription monitoring databases, and perhaps randomly checking urine drug screens. Alprazolam should be discontinued much more slowly than the manufacturer guidelines suggest. A reasonable guideline (Pecknold et al., 1988) is to not to exceed 0.125 mg weekly and over a period of at least 8 weeks (Risse et al., 1990). It could be substituted with a faster taper of a longer-acting benzodiazepine such as clonazepam, using clonidine and/or carbamazepine augmentation. Gabapentin is another option that should be considered during alprazolam discontinuation to prevent rebound anxiety, cravings, and other withdrawal symptoms.

When prescribing alprazolam, clinicians should discuss the treatment plan or consider using a formalized written treatment agreement, which both educates patients about the risks of benzodiazepines use and clarifies expectations, including the short-term nature of the prescription. Many providers feel pressurized by their patients to continue prescribing as they try to wean them off benzodiazepines, and more-so with alprazolam, given the positive subjective drug effects. Alprazolam should not be prescribed at a higher dose than is US FDA-recommended, and providers should consider discontinuation if patients are requesting higher doses, as it may signal therapeutic tolerance and/or misuse.

Well-designed human studies addressing alprazolam's reinforcing effects and the discontinuation syndrome are needed, and must consider important issues such as selection of appropriate comparison drug, dose, formulation, and population. Future research should also further investigate the misuse liability of alprazolam XR, and should attempt to clarify the role of carbamazepine, clonidine, other anticonvulsant drugs, and related compounds in the treatment of the alprazolam withdrawal syndrome.

REFERENCES

ACOG. American College of Obstetricians and Gynecologists Practice Bulletin No. 87 November 2007: Use of psychiatric medications during pregnancy and lactation. *Obstet Gynecol* 2007;110:1179.

Adler LE, Bell J, Kirch D, et al. Psychosis associated with clonidine withdrawal. *Am J Psychiatry* 1982;139:110–112.

Albeck JH. Withdrawal and detoxification from benzodiazepine dependence: a potential role for clonazepam. *J Clin Psychiatry* 1987;48(Suppl):43–48.

Altshuler L, Cohen L. Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. *Year Book Psychiatry Appl Mental Health* 1997;1997:491.

Apelt S, Schmauss C, Emrich H. Preference for alprazolam as opposed to diazepam in benzodiazepine-dependent psychiatric inpatients. *Pharmacopsychiatry* 1990;23:70–75.

Baldwin DS, Polkinghorn C. Evidence-based pharmacotherapy of generalized anxiety disorder. *Int J Neuropsychopharmacol* 2005;8:293–302.

Ballenger JC, Burrows GD, DuPont RL, et al. Alprazolam in panic disorder and agoraphobia: Results from a multicenter trial: I. Efficacy in short-term treatment. *Arch Gen Psychiatry* 1988;45:413–422.

Bandelow B, Zohar J, Hollander E, et al., WFSBP Task Force on Treatment Guidelines for Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders. *World J Biol Psychiatry* 2008;9:248–312.

Barker MJ, Greenwood KM, Jackson M, et al. Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. *Arch Clin Neuropsychol* 2004;19:437–454.

Bentue-Ferrer D, Reymann J, Tribut O, et al. Role of dopaminergic and serotonergic systems on behavioral stimulatory effects of low-dose alprazolam and lorazepam. *Eur Neuropsychopharmacol* 2001;11:41–50.

Björkqvist SE, Isohanni M, Mäkelä R, et al. Ambulant treatment of alcohol withdrawal symptoms with carbamazepine: a formal multicentre double-blind comparison with placebo. *Acta Psychiatr Scand* 1976;53:333–342.

Browne J, Hauge K. A review of alprazolam withdrawal. *Drug Intelligence Clin Pharm* 1986;20:837–841.

Centers for Disease Control and Prevention. Drug overdose deaths: Florida, 2003–2009. *MMWR* 2011;60:869–872.

Ciraulo DA, Barnhill JG, Ciraulo AM, et al. Alterations in pharmacodynamics of anxiolytics in abstinent alcoholic men: subjective responses, abuse liability, and electroencephalographic effects of alprazolam, diazepam, and buspirone. *J Clin Pharmacol* 1997;37:64–73.

Curran HV, Bond A, O'Sullivan G, et al. Memory functions, alprazolam and exposure therapy: a controlled longitudinal study of agoraphobia with panic disorder. *Psychol Med* 1994;24:969–976.

Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci USA* 1988;85:5274–5278.

Dilsaver SC, Peck JA, Traumata D, et al. Treatment with carbamazepine may enhance (2-noradrenergic autoreceptor sensitivity. *Biol Psychiatry* 1993;34:551–557.

Dolovich LR, Addis A, Vaillancourt JR, et al. Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. *BMJ* 1998;317:839–843.

Eriksson E, Carlsson M, Nilsson C, et al. Does alprazolam, in contrast to diazepam, activate alpha2-adrenoceptors involved in the regulation of rat growth hormone secretion? *Life Sci* 1986;38:1491–1498.

Freiberger JJ, Marsicano TH. Alprazolam withdrawal presenting as delirium after cardiac surgery. *J Cardiothorac Vasc Anesth* 1991;5:150–152.

Fyer AJ, Liebowitz MR, Gorman JM, et al. Discontinuation of alprazolam treatment in panic patients. *Am J Psychiatry* 1987;144:303–308.

Fyer AJ, Liebowitz MR, Gorman JM, et al. Effects of clonidine on alprazolam discontinuation in panic patients: a pilot study. *J Clin Psychopharmacol* 1988;8:270–274.

Galpern WR, Miller LG, Szabo GK, et al. Chronic benzodiazepine administration: IX. Attenuation of alprazolam discontinuation effects by carbamazepine. *Biochem Pharmacol* 1991;42:99–104.

Greenblatt DJ, Wright CE. Clinical pharmacokinetics of alprazolam. *Clin Pharmacokinet* 1993;24:453–471.

Griffiths RR, Wolf B. Relative abuse liability of different benzodiazepines in drug abusers. *J Clin Psychopharmacol* 1990;10:237–243.

Grohol J, 2016. Top 25 Psychiatric Medication Prescriptions for 2013. Available at: https://psychcentral.com/lib/top-25-psychiatric-medication-prescriptions-for-2013/.

Heh CW, Sramek J, Herrera J, et al. Exacerbation of psychosis after discontinuation of carbamazepine treatment. *Am J Psychiatry* 1988; 145:878–879.

Henderson A, Wright M, Pond S. Experience with 732 acute overdose patients admitted to an intensive care unit over six years. *Med J Australia* 1993; 158:28–30.

Iguchi MY, Griffiths RR, Bickel WK, et al. Relative abuse liability of benzodiazepines in methadone maintained populations in three cities. *NIDA Res Monograph* 1989;95:364–365.

Iqbal MM, Sobhan T, Ryals T. Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. *Psychiatr Serv* 2002;53:39–49.
Isbister GK, O'regan L, Sibbritt D, et al. Alprazolam is relatively more toxic than other benzodiazepines in overdose. *Br J Clin Pharmacol* 2004;58: 88–95.
Jonas JM, Cohon MS. A comparison of the safety and efficacy of alprazolam versus other agents in the treatment of anxiety, panic, and depression: a review of the literature. *J Clin Psychiatry* 1993;54(Suppl 25–45):46–48.
Juergens S. Alprazolam and diazepam: addiction potential. *J Subst Abuse Treatment* 1991;8:43–51.
Kales A, Soldatos CR, Bixler EO, et al. Diazepam: effects on sleep and withdrawal phenomena. *J Clin Psychopharmacol* 1988;8:340–346.
Kantor SJ. A difficult alprazolam withdrawal. *J Clin Psychopharmacol* 1986;6:124–125.
Klein E, Uhde TW, Post RM. Preliminary evidence for the utility of carbamazepine in alprazolam withdrawal. *Am J Psychiatry* 1986;143: 235–236.
Klerman GL. Overview of the cross-national collaborative panic study: I. efficacy in short-term treatment. *Arch Gen Psychiatry* 1988;45:407–412.
Kroll DS, Nieva HR, Barsky AJ, et al. Benzodiazepines are prescribed more frequently to patients already at risk for benzodiazepine-related adverse events in primary care. *J Gen Intern Med* 2016;31(9):1027–1034.
Laegreid L, Olegrd R, Walström J, et al. Teratogenic effects of benzodiazepine use during pregnancy. *J Pediatr* 1989;114:126–131.
Levenson JL. The American Psychiatric Publishing Textbook of Psychosomatic Medicine: Psychiatric Care of the Medically Ill. 2nd ed, Arlington, Virginia: American Psychiatric Pub; 2011.
Lucki I, Rickels K. The behavioral effects of benzodiazepines following long-term use. *Psychopharmacol Bull* 1986;22:424.
Lucki I, Rickels K, Geller AM. Chronic use of benzodiazepines and psychomotor and cognitive test performance. *Psychopharmacology* 1986;88: 426–433.
McKenzie RR, Jr Madadi P, Sharma TR. Alprazolam withdrawal delirium and brief reversible psychosis: a case report. *Prim Care Companion CNS Disord* 2014;16.
Moylan S, Staples J, Ward SA, et al. The efficacy and safety of alprazolam versus other benzodiazepines in the treatment of panic disorder. *J Clin Psychopharmacol* 2011;31:647–652.
Mumford G, Evans S, Fleishaker J, et al. Alprazolam absorption kinetics affects abuse liability. *Clin Pharmacol Therapeut* 1995;57:356–365.
National Collaborating Centre for Mental Health. Antenatal and postnatal mental health: clinical management and service guidance—updated edition. NICE guideline (CG192). London, UK: British Psychological Society and The Royal College of Psychiatrists; 2014.
Nutt DJ. Overview of diagnosis and drug treatments of anxiety disorders. *CNS Spectrums* 2005;10:49–56.
Orzack MH, Friedman L, Dessain E, et al. Comparative study of the abuse liability of alprazolam, lorazepam, diazepam, methaqualone, and placebo. *Int J Addict* 1988;23:449–467.
Páll A, Becs G, Erdei A, et al. Pseudopheochromocytoma induced by anxiolytic withdrawal. *Eur J Med Res* 2014;19:53.
Patterson JF. Withdrawal from alprazolam dependency using clonazepam: clinical observations. *J Clin Psychiatry* 1990;51(5, Suppl):47–49.
Pecknold JC, Swinson RP, Kuch K, et al. Alprazolam in panic disorder and agoraphobia: Results from a multicenter trial: III. Discontinuation effects. *Arch Gen Psychiatry* 1988;45:429–436.
Penders T. Gabapentin (Neurontin): an adjunct for benzodiazepine withdrawal. *Ommega Internations* 2015;1:1–8.
Rickels K, Schweizer E, Garcia Espana F, et al. Trazodone and valproate in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal symptoms and taper outcome. *Psychopharmacology* 1999; 141:1–5.
Risse SC, Whitters A, Burke J, et al. Severe withdrawal symptoms after discontinuation of alprazolam in eight patients with combat-induced posttraumatic stress disorder. *J Clin Psychiatry* 1990;51:206–209.
Sachdev G, Gesin G, Christmas AB, et al. Failure of lorazepam to treat alprazolam withdrawal in a critically ill patient. *World J Crit Care Med* 2014;3:42.
SAMHSA. Drug Abuse Warning Network, 2011: national estimates of drug-related emergency department visits. *Subst Abuse Mental Health Serv Administr* 2013;13:4760.
Schmauss C, Apelt S, Emrich H. The seeking and liking potentials of alprazolam. *Am J Psychiatry* 1988;145. 128a-128.
Schmauss C, Apelt S, Emrich H. Preference for alprazolam over diazepam. *Am J Psychiatry* 1989;146:408.
Schweizer E, Rickels K, Weiss S, et al. Maintenance drug treatment of panic disorder: I. Results of a prospective, placebo-controlled comparison of alprazolam and imipramine. *Arch Gen Psychiatry* 1993;50:51–60.
Tollefson GD. Hyperadrenergic hypomania consequent to the abrupt cessation of clonidine. *J Clin Psychopharmacol* 1981;1:93–95.
van Marwijk H, Allick G, Wegman F, et al. Alprazolam for depression. *Cochrane Database Syst Rev* 2012;CD007139.
Vander Weele CM, Porter-Stransky KA, Mabrouk OS, et al. Rapid dopamine transmission within the nucleus accumbens: dramatic difference between morphine and oxycodone delivery. *Eur J Neurosci* 2014;40:3041–3054.
Vinogradov S, Reiss A, Csernansky J. Clonidine therapy in withdrawal from high-dose alprazolam treatment. *Am J Psychiatry* 1986;143:1188.
White FJ, Kalivas PW. Neuroadaptations involved in amphetamine and cocaine addiction. *Drug Alcohol Depend* 1998;51:141–153.
Willuhn I, Wanat MJ, Clark JJ, et al. Dopamine signaling in the nucleus accumbens of animals self-administering drugs of abuse. *Behav Neurosci Drug Addict* 2010;3:29–71.
Wolf B, Iguchi MY, Griffiths RR. Sedative/tranquilizer use and abuse in alcoholics currently in outpatient treatment: incidence, pattern and preference. *NIDA Res Monograph* 1989;95:376–377.
Yonkers KA, Wisner KL, Stowe Z, et al. Management of bipolar disorder during pregnancy and the postpartum period. *Am J Psychiatry* 2004; 161:608–620.
Zalsman G, Hermesh H, Munitz H. Alprazolam withdrawal delirium: a case report. *Clin Neuropharmacol* 1997;21:201–202.
Zipursky RB, Baker RW, Zimmer B. Alprazolam withdrawal delirium unresponsive to diazepam: case report. *J Clin Psychiatry* 1985;46:344–345.