THE CARLAT REPORT
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Benjamin Oldfield, MD, MHS
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Emerging Risks for Old Medications

Learning Objectives
After reading these articles, you should be able to:

1. Characterize the hazards of non-benzodiazepine sedative-hypnotic medications ("Z-drugs").
2. Assess for and treat the unhealthy use of benzodiazepines and gabapentinoids.
3. Describe the mechanisms, side effects, and risks of commonly prescribed muscle relaxants.
4. Summarize some of the findings in the literature regarding addiction treatment.

The "Z-Drugs": Safety Issues and Misuse Potential

Reban Aziz, MD. Associate Professor of Psychiatry and Neurology, Rutgers Robert Wood Johnson Medical School.

Dr. Aziz has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Originally marketed as safer alternatives to benzodiazepines, the Z-drugs—eszopiclone (Lunesta), zaleplon (Sonata), and zolpidem (Ambien)—were considered devoid of misuse potential. But recent data and FDA warnings suggest we've been hitting the snooze on them for too long. Here, we review their risks and discuss safe prescribing.

Medical risks
Zolpidem is the most widely prescribed hypnotic in the US and was the fourth most frequently prescribed psychiatric drug in 2013 (Moore TJ and Mattison DR, *JAMA Intern Med* 2017;177(2):274–275). Although generally recommended

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Highlights From This Issue

Non-benzodiazepine sedative-hypnotic drugs ("Z-drugs") and muscle relaxants are commonly prescribed off-label and are associated with adverse events including overdose.

Dr. Vickers-Smith discusses alarming increases in gabapentinoid use and misuse, and Dr. Morford characterizes his approach to benzodiazepine use in addiction treatment settings.

In the first randomized controlled trial of baclofen titrated to high doses for the treatment of alcohol use disorder, the intervention arm had decreased alcohol use but considerable adverse events.

Q&A With the Expert

Gabapentin Misuse and Diversion

Rachel Vickers-Smith, PhD, MPH

Assistant Professor at University of Louisville, KY.

Dr. Vickers-Smith has disclosed that she has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CATR: Could you start by telling us a little bit about yourself and your current work?
Dr. Vickers-Smith: I am an epidemiologist, and my work has primarily been on gabapentin as an emerging drug of recreational and unhealthy use. This interest came about while I was working for Dr. Jennifer Havens on her cohort of about 500 individuals in central Appalachia: the epicenter of the opioid epidemic. The cohort included individuals who mostly used non-medical prescription opioids. She had been following them since 2008, asking what kind of drugs they were using and how they were using them. In this group we noticed an uptick in people starting to report gabapentin misuse. From that stemmed a larger body of research trying to

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understand if this was unique to eastern Kentucky or central Appalachia, or if this was a much larger issue.

CATR: Fascinating. What do we know about the prevalence of gabapentinoid misuse?

Dr. Vickers-Smith: Gabapentinoids, which include the medications gabapentin and pregabalin, work by inhibiting voltage-dependent calcium channels (even though they are analogues of the inhibitory neurotransmitter GABA, they don't bind to GABA receptors). In the general population, gabapentin misuse is uncommon. There's been only one study to estimate overall population prevalence—in the United Kingdom—and that was 1%. But our research has shown that gabapentinoid misuse has a far higher prevalence among people with unhealthy substance use. Our best estimates are that between 15% and 22% of this population misuse gabapentin (Smith RV et al, *Addiction* 2016;111(7):1160–1174). And it's possible that those are underestimates. Until recently, the research and clinical communities have not been asking about gabapentinoid misuse.

"In our cohort in eastern Kentucky between 2008 and 2014, we saw a nearly 3,000% increase in recreational use of gabapentin. Almost certainly, that wasn't unique to eastern Kentucky. That's been observed throughout the country, as well. And we think that the prevalence is not falling."

Rachel Vickers-Smith, PhD, MPH

CATR: Has this evolved in recent years?

Dr. Vickers-Smith: In our cohort in eastern Kentucky between 2008 and 2014, we saw a nearly 3,000% increase in recreational use of gabapentin (Smith RV et al, *Am J Psychiatry* 2015;172(5):487–488). Almost certainly, that wasn't unique to eastern Kentucky. That's been observed throughout the country, as well. And we think that the prevalence is not falling. At most, perhaps at this point, it's stabilizing, since across the country we're seeing a lot of policy behind gabapentin scheduling and prescribing. There are 22 states that have scheduled gabapentin, are discussing scheduling gabapentin in their state legislature, or have noted gabapentin as a drug of concern and are requiring it to be reported to the prescription drug monitoring programs. This is an indication that we weren't just looking at a flash in the pan, that there has been increasing misuse, and that we are now at the point where we're needing to do something at a policy level.

CATR: Those are staggering figures. What makes gabapentinoids an attractive drug for some people?

Dr. Vickers-Smith: Yes, that's the million-dollar question, because when gabapentin was released, it was presumed to have no abuse potential. However, we're seeing two major reasons that people report gabapentin misuse (Vickers-Smith R et al, *Psychol Addict Behav* 2018;32(1):115–121). One is recreationally. The other is to self-medicate. When people use it recreationally, they report super-therapeutic doses and also typically use it with other substances. For example, they might break capsules in half and drink them with a cup of coffee or an energy drink, and it may give them the feeling of a speedball (ie, a depressant and stimulant together, such as heroin and cocaine). Others have said that they use it in combination with opioids to potentiate the high that they experience from the opioids, or to prolong the effect of the opioids. We've also heard people say that gabapentin may help them to achieve a high off of their methadone or buprenorphine treatment. These are all anecdotal, self-reported experiences. People have also reported misusing it with alcohol, marijuana, or cocaine.

CATR: You also mentioned it is often used to self-medicate.

Dr. Vickers-Smith: People have said that if they're coming down off of, say, opioids, they can use gabapentin and it helps with the comedown. It also may help stave off withdrawal or alleviate the pain of withdrawal. Others have reported that they may not be able to access opioids for their pain anymore, so gabapentin has helped with their pain. Another thing to keep in mind

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SAMHSA Relaxes Regulations on Methadone and Buprenorphine During COVID-19 Emergency

Benjamin Oldfield, Editor-in-Chief of CATR. *Clinical Instructor in Medicine and Pediatrics at Yale School of Medicine; Chief Medical Officer at Fair Haven Community Health Care, CT.*

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The Substance Abuse and Mental Health Services Administration (SAMHSA) has changed some prescribing rules to help minimize in-person contact while maintaining access to medications for opioid use disorder (OUD).

Methadone

Patients starting methadone continue to require an in-person medical evaluation at an opioid treatment program (OTP) prior to starting the medication. However, patients already on methadone can receive their ongoing care via telemedicine visits. Furthermore, OTPs can now more easily provide take-home doses. Take-home doses are now allowed for up to 14 days for "clinically less stable" patients and 28 days for "clinically stable" patients. The definition of stability is left to the OTP. For example, SAMHSA characterizes those eligible for 14 days as "less stable but whom the OTP believes can safely handle this level of take-home medication."

Buprenorphine

Patients no longer need in-person visits prior to starting buprenorphine. If you determine that an adequate evaluation of the patient can be accomplished via telemedicine, this is sufficient. Ongoing care can also occur via telemedicine.

Monitoring

Current federal regulations still require that each patient receives 8 urine toxicology tests per year. However, new guidelines acknowledge that we should not require patients to come into the clinic for testing if they have symptoms of COVID-19 or if they have had close contact with someone who has the infection.

For further reading, please see: www.samhsa.gov/coronavirus

CATR VERDICT: The government is taking appropriate measures to allow and expand treatment for OUD while reducing the spread of COVID-19. Addiction providers should explore telemedicine options that support patients with OUD given recent increases in social isolation, job loss, and anxiety, all of which may worsen the burden of OUD. Because your patients may have larger than normal doses of methadone or buprenorphine at home, you should discuss safe storage practices, provide overdose education, and distribute naloxone.

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is that, while people have reported that prolonged use has negative effects, they're not as severe as for opioids. So, people may experience withdrawal from gabapentin, but it's nothing like an opioid withdrawal—it's more manageable and generally consists of irritability. It may not last as long. The fact that there are few negative effects, especially in comparison to other more commonly abused drugs, makes gabapentin more desirable. Finally, people report that it's cheap and they're nearly always able to get it. Those features have also facilitated the misuse of gabapentin.

CATR: You alluded to gabapentin's interesting relationship with the opioid epidemic. How are gabapentinoids implicated in opioid-related deaths?

Dr. Vickers-Smith: Epidemiological evidence seems to suggest an interaction between gabapentin and opioids. We have seen an increase in opioid-related mortality in the presence of gabapentin. Presumably, gabapentin increases the risk of opioid-related overdoses by potentiating CNS and respiratory depression. Just in December 2019, the FDA issued a warning about gabapentinoids and has mandated that drug manufacturers go back to the laboratory and conduct clinical trials that evaluate the abuse potential of gabapentinoids, particularly in combination with opioids and paying special attention to respiratory depression. So, while early evidence and intuition suggest that this class of medications potentiates the CNS and respiratory depression that drives opioid-related overdoses, we need to go into the laboratory to understand what is actually going on and better understand the dose response, as well.

CATR: What can clinicians do to promote safer and more judicious use of gabapentinoids?

Dr. Vickers-Smith: First of all, simply being aware that there is abuse potential for gabapentinoids helps. Second, if prescribing gabapentinoids, consider if your patient is at risk for misuse or diversion. Finally, monitor for misuse. Are there escalating doses? Are there requests for early refills? Is there evidence of diversion? We also need to engage in conversations about the risks of fatal overdose when combining gabapentin and opioids. In a recent study out of Miami, researchers found that many people initiated gabapentin misuse in addiction treatment and transitional living facilities (Buttram ME et al, *Drug Alc Depend* 2019;204:107554). So, it may be that people are wanting to experience a high, but they don't have access to their preferred drug of abuse.

CATR: Do we contribute to the problem by prescribing it so often?

Dr. Vickers-Smith: Because gabapentin is not federally scheduled, there aren't as many barriers for patients to receive prescriptions as there are for other drugs of abuse. I've heard multiple stories of people going in and asking a provider for gabapentin and getting a prescription for it. Or, they have a family member who was prescribed gabapentin for something, and they just have lots of it lying around and so they can easily access it. In fact, the majority of gabapentin use is off-label—83%

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for short-term use, a national study in 2018 demonstrated that greater than two-thirds of patients prescribed zolpidem took it for longer than 3 months (Moore TJ and Mattison DR, *JAMA Intern Med* 2018;178(9):1275–1277).

Zolpidem has been associated with several side effects. From 2009 to 2011, it was implicated in 12% of all adult ED visits due to adverse drug events from psychiatric medications and in 21% of such visits involving adults 65 years or older. In both cases, this was significantly more than any other psychiatric medication. Adverse events included falls, head injuries, sedation, vertigo, and confusion (Hampton LM et al, *JAMA Psychiatry* 2014;71(9):1006–1014). Falls are a major concern in older adults, and unfortunately, zolpidem significantly increases the odds of a fracture (Kang DY et al, *J Prev Med Public Health* 2012;45(4):219–226).

Complex sleep behaviors

Z-drugs have been connected to complex sleep behaviors. Examples include sleepwalking, sleep driving, and even things like sleep cooking, sleep eating, or other unsafe actions. The FDA has received reports of people accidentally overdosing, falling, getting burned, shooting themselves, and wandering outside in cold weather. The absolute number of reported events is low, however. Between 1992 and 2019, there were 66 serious cases of complex sleep behaviors, 20 of which resulted in death; that said, the actual number of cases is likely higher as these figures only include cases voluntarily reported to the FDA as well as 4 published cases (www.fda.gov/consumers/consumer-updates/taking-z-drugs-insomnia-know-risks).

Motor vehicle accidents

There is an increased risk of motor vehicle accidents in patients prescribed benzodiazepines and hypnotics. The FDA has noted that zolpidem blood levels above 50 ng/mL appear capable of impairing driving to a degree that increases accident risk. The FDA found that 15% of women and 3% of men had zolpidem concentrations exceeding 50 ng/mL 8 hours after taking 10 mg of zolpidem. An even higher percentage of men (25%) and women (33%) experienced potentially impairing morning zolpidem levels after using 12.5 mg of extended-release zolpidem products (www.fda.gov/media/84992/download). These findings led to changes in the labeling and dosing of zolpidem.

Risk of addiction, withdrawal, and overdose

Benzodiazepines still carry a higher risk of misuse and withdrawal than the Z-drugs, though Z-drug use disorders have been reported. Risk factors for Z-drug addiction include a history of drug use disorders and/or psychiatric illness (Hajak G et al, *Addiction* 2003;90(10):1371–1378).

While these risks appear to be shared by all Z-drugs, zolpidem appears to confer a greater risk of withdrawal than zopiclone or eszopiclone. More prolonged use of zolpidem is also associated with greater likelihood of withdrawal. Symptoms of Z-drug withdrawal include insomnia, anxiety, euphoria, irritability, tremor, restlessness, speech difficulties, abdominal pain, hypertension, seizures, and delirium (Schifano F et al, *Int J Neuropsychopharmacol* 2019;22(4):270–277).

Z-drugs carry a risk of overdose. This may be greater with zolpidem and zopiclone than zaleplon (Schifano F et al, 2019). Overdose risk may be particularly high when Z-drugs are combined with opioids. The risk of an opioid overdose when Z-drugs are used with opioids seems to be about the same as when benzodiazepines are mixed with opioids. Overall, patients exposed to opioids, benzodiazepines, and non-benzodiazepine sedative-hypnotics at any point are 60% more likely to overdose than those only exposed to opioids (Cho J et al, *J Gen Intern Med* 2020;35:696–703).

What can clinicians do?

Clinicians can reduce adverse Z-drug events by limiting them to short-term use for insomnia, and only turning to Z-drugs after considering other treatments such as sleep hygiene education, stimulus control therapy, sleep restriction therapy, relaxation strategies, cognitive behavioral therapy for insomnia (CBT-I), and safer medication alternatives. If zolpidem is to be used, warn your patients about the risk of next-morning impairment for activities requiring alertness, like driving. Patients should also know that impairment can occur even if they feel fully awake. Tell patients to take their medication immediately before bed with at least 7–8 hours of planned sleeping time.

The FDA has updated the labeling for zolpidem to reduce the risk of next-morning impairment (see table below).

Updated FDA Dosing Recommendations for Zolpidem

Drug	New Dosing Recommendations
Zolpidem	Women: 5 mg nightly Men: 5–10 mg nightly Elderly: 5 mg nightly
Extended-release zolpidem	Women: 6.25 mg nightly Men: 6.25–12.5 mg nightly Elderly: 6.25 mg nightly

Source: www.fda.gov/media/84992/download

CATR VERDICT: Prescribe Z-drugs with caution, especially with patients who are older, have comorbid psychiatric illnesses, and/or have a history of substance use disorders. Educate patients about complex sleep-related behaviors and avoid using Z-drugs if they've experienced such behaviors in the past. If Z-drugs are prescribed, use them short-term or intermittently, and regularly evaluate their continued use.

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Muscle Relaxants: Sedatives Often Under the Radar

Michael Weaver, MD, FASAM. Professor and medical director at the Center for Neurobehavioral Research on Addictions at the University of Texas Medical School. Author of Addiction Treatment *(Carlat Publishing, 2017).*

Dr. Weaver has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Muscle relaxants are a diverse group of medications with varying mechanisms of action (see Commonly Prescribed Muscle Relaxants table below). They are indicated for short-term treatment (2–3 weeks) of acute, painful muscle spasms, as well as some chronic neurologic conditions associated with spasticity. However, many patients with chronic pain are on them for years, despite little data about long-term safety or efficacy (van Tulder MW et al, *Cochrane Database Syst Rev* 2003(2);CD004252). Prescriptions for muscle relaxants are likely on the rise due to recent CDC guidelines for the management of chronic pain that emphasize non-opioid medications (Dowell D et al, *MMWR Recomm Rep* 2016;65(1):1–49).

All muscle relaxants may be sedating, which poses increased risks when combined with other medications for chronic pain, psychiatric disorders, or addiction treatment. Different muscle relaxants are thought to have similar efficacy, so choose one based on side effects, drug interactions, and abuse potential (Chou R et al, *J Pain Symptom Manage* 2004;28(2):140–175).

Baclofen, tizanidine, and cyclobenzaprine cause withdrawal syndromes if stopped abruptly, so tapering is recommended. Tizanidine may lower blood pressure, so it should be used with caution in patients at risk for hypotension or bradycardia due to other medical conditions or medications. Keep in mind, too, that baclofen may be prescribed for the management of alcohol use disorder (see Research Update on page 9).

Carisoprodol (Soma) is especially risky for patients with substance use disorders or who use sedatives—whether therapeutically or recreationally. Many prescribers are unaware that the liver metabolizes carisoprodol to meprobamate, which used to be marketed as Miltown or Equanil. Meprobamate has sedative effects similar to barbiturates and can cause respiratory depression, euphoria, and anxiolysis. Since carisoprodol is not an obvious sedative, it is often sought by patients seeking to achieve a high or to manage anxiety, and may end up on the black market. It is classified as a Schedule IV controlled substance, so it is often tracked by state prescription monitoring programs. Nearly all cases of addiction to muscle relaxants are due to carisoprodol, although cyclobenzaprine has also been associated with misuse.

Ten percent of patients prescribed opioids are also prescribed muscle relaxants (Mosher HJ et al, *Pain Med*

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Commonly Prescribed Muscle Relaxants

Muscle Relaxant	Brand Name	Mechanism of Action	Typical Dosing	Side Effects	Cautions
Baclofen	Lioresal	Presynaptic GABA-B agonist	5–20 mg every 6 hrs	Sedation Confusion Dizziness Nausea	Abrupt discontinuation can cause seizure
Carisoprodol	Soma	CNS depression	250–350 mg every 6 hrs	Sedation Headache	Causes tolerance, withdrawal, and addiction Schedule IV controlled substance Not approved for under age 16
Cyclobenzaprine	Flexeril Amrix	Tricyclic agent (related to amitriptyline)	Immediate release: 5–10 mg every 8 hrs Extended release: 15 mg daily Extended release: 15 mg daily (max 30 mg/24 hrs)	Sedation Dizziness Blurred vision Dry mouth	Withdrawal syndrome (nausea, headache, general discomfort) May cause serotonin syndrome in combination with SSRIs, SNRIs, bupropion, tramadol, etc.
Metaxalone	Skelaxin	CNS depression	800 mg every 6–8 hrs	Sedation Nausea Irritability	Gastrointestinal absorption increased with food and older age
Methocarbamol	Robaxin	CNS depression	750 mg every 4 hrs, 1500 mg every 6 hrs (max 8000 mg/24 hrs)	Headache Dizziness Sedation	Sedating
Orphenadrine	Norflex Banflex Flexon	Central atropine-like anticholinergic effects (related to diphenhydramine)	100 mg every 12 hrs	Dry mouth Blurred vision Constipation Sedation	Euphorigenic properties
Tizanidine	Zanaflex	Central alpha-2 adrenergic agonist	2–16 mg every 6–8 hrs (max 36 mg/24 hrs)	Sedation Dizziness Hypotension Bradycardia Elevated transaminases	Withdrawal syndrome that includes elevated blood pressure and heart rate Hallucinations and psychosis in 3% of patients

Q&A With the Expert

Benzodiazepines: Old Medicines, New Concerns

Kenneth Morford, MD

Assistant Professor and Program Director, Collaborative Behavioral Health & Addiction Medicine in Primary Care (CHAMP) at Yale School of Medicine.

Dr. Morford has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CATR: To begin, tell us about the research and clinical work you do.
Dr. Morford: I am an assistant professor at the Yale School of Medicine in the Program of Addiction Medicine. I trained as a general internist, and I see patients primarily at a large opioid treatment program and in an inpatient setting on an addiction consult service. I'm involved in a number of addiction-focused research and educational activities, and I teach trainees in various levels in nursing, physician associate, and medical schools.
CATR: You've done research on benzodiazepine use, and I imagine it comes up often clinically for you, too. How prevalent is benzodiazepine use?
Dr. Morford: According to the National Survey on Drug Use and Health, about 12.5% of US adults have used benzodiazepines for prescription and non-medical use in the past year (Maust DT et al, *Psychiatric Services* 2019;70(2):97–106). If we're looking at prescribed benzodiazepines, we've seen an increase over the past decade or two. One study of data from the National Ambulatory Medical Care Survey showed that in 2003, 3.8% of ambulatory visits involved benzodiazepine prescriptions in the US, and that increased to 7.4% in 2015 (Agarwal SD and Landon BE, *JAMA Network Open* 2019;2(1):e187399). So, we are seeing increased prescribing of benzodiazepines. In terms of misuse, it's estimated that a little over 2% of the US population reports misusing benzodiazepines.
CATR: While the story of increases in opioid prescribing has been told, increased use of benzodiazepines is less well characterized. What are your thoughts?
Dr. Morford: I don't think it's as well understood as what we saw with opioid prescribing and the role of the pharmaceutical industry in that. What we do know is that the percentage of benzodiazepine prescriptions by psychiatrists has remained relatively stable at around 30% over that time period I talked about from 2003 to 2015, while prescriptions of benzodiazepines by several other physician groups increased. And that includes primary care physicians, who account for more than 50% of all benzodiazepine prescriptions (Agarwal and Landon, 2019).
CATR: Many patients have been prescribed benzodiazepines for years. How should we approach them?
Dr. Morford: For patients who come into my clinic who've already been receiving benzodiazepines for a number of years, my first step is to determine the indication and clarify the diagnosis that they were prescribed for. Typically, we will see that benzodiazepines were prescribed for anxiety and for insomnia, without evidence of ongoing or recent use of first-line medication treatments for these disorders.
CATR: And the next step?
Dr. Morford: You'll want to ask about side effects; this can be educational for patients. Ask your patient if they have experienced sedation, dizziness, and/or falls. Also, have they experienced withdrawal symptoms if they decreased or stopped taking their usual dose? Some patients may perceive the anxiety of inter-dose withdrawal (or otherwise when attempting to taper) as evidence that the taper is a failure or that they have an underlying anxiety disorder, when they may simply be exhibiting mild withdrawal. Lastly, assessing for other psychoactive or sedating substance use is important to understand risk. This can include alcohol and opioids, but also substances that may go under the radar, like antihistamines, muscle relaxants, or gabapentinoids.
CATR: You mentioned benzodiazepine-related risks. Some people are calling benzodiazepines the "new opioids." Are we entering a benzodiazepine crisis?
Dr. Morford: I think that it's important to recognize the differences between benzodiazepines and opioids. First of all, in terms of some of their differences, benzodiazepines are considered a safer medication largely because they do not impact respiratory depression the same way that opioids do. Benzodiazepines are a Schedule IV controlled substance, as opposed to opioids that are Schedule II. But benzodiazepines clearly do have potential for misuse, similar to opioids. And we see that there are serious risks of benzodiazepine use, especially when combined with other CNS depressants like opioids or alcohol (Jones JD et al, *Drug Alcohol Depend* 2012;125(1–2):8–18; Hernandez I et al, *JAMA Network Open* 2018;1(2):e180919). One recent national study demonstrated that benzodiazepine co-involvement in opioid-related overdoses has increased over the last two decades; benzodiazepines were involved in 21% of such deaths in 2017 (Tori ME et al, *JAMA Network Open* 2020;3(4):e202361). Finally, a major risk of chronic benzodiazepine use is the development of physical dependence that leads to risk of withdrawal, which can include life-threatening events such as seizures.
CATR: Given the risks of combining CNS depressants, what clinical considerations should we keep in mind when seeing patients who are prescribed benzodiazepines and who also have opioid use or alcohol use disorder?
Dr. Morford: This is an important question and is very relevant to my clinical practice. Most of my patients have substance use disorders and may come to me already receiving a benzodiazepine prescription. Most importantly, especially for

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patients with opioid use disorder, we don't withhold medications for opioid use disorder, such as methadone and buprenorphine, simply because a patient is also taking a benzodiazepine. This is consistent with the recently released ASAM Guidelines for the Management of Opioid Use Disorder (Crotty K et al, *J Addict Med* 2020;14:99–112). The other important consideration here is making sure that patients with opioid use disorder are receiving an adequate dose of those medications. Oftentimes, I'll see that patients are receiving a lower dose of methadone or buprenorphine because the provider is worried about the concurrent use of benzodiazepines, and that can bring patients to use benzodiazepines as a way to self-medicate withdrawal symptoms. We may be setting those patients up to fail. So, one of my first steps is to make sure that the methadone or buprenorphine dose is adequate.

CATR: Do you ever question the need for the benzodiazepine in the first place, or discuss tapering?

Dr. Morford: If a patient is receiving benzodiazepines from another prescriber and not receiving first-line therapy, it's important to connect with that other provider to discuss the case and come up with a coordinated plan. Despite limited data, current guidelines recommend that we taper benzodiazepines to discontinuation, especially for patients who have co-occurring substance use disorders, and this is the approach I try to take (SAMHSA, Tip 63: Medications for Opioid Use Disorder; www.tinyurl.com/y7kbv6ot). The benefits of a taper, when successful, can be enormous: less risk for sedation, of course, but patients can also report functional improvement, more clarity in thinking, and improved sleep over time. The risks, however, generally apply to overly rapid tapers, which can produce withdrawal symptoms—including irritability and insomnia—and can also encourage patients to disengage from care if they're not convinced the taper is in their best interest.

> **"Especially for patients with opioid use disorder, we don't withhold medications such as methadone and buprenorphine simply because a patient is also taking a benzodiazepine. This is consistent with the recently released ASAM Guidelines for the Management of Opioid Use Disorder."**
>
> Kenneth Morford, MD

CATR: So the guidelines suggest that we should not withhold treatment for opioid use disorder because of benzodiazepine use. However, if we do go down that route, we should strongly consider a benzodiazepine taper.

Dr. Morford: Yes. You may be familiar with the FDA's initial communication in 2016 that prescribers should avoid combining benzodiazepines and opioids at all costs. However, there wasn't clear guidance on what to do with medications like methadone and buprenorphine that are opioids but are being used to treat opioid use disorder. So a year later in 2017, the FDA came out with an updated statement that clearly said that we should not withhold those medications from patients who are taking benzodiazepines, but have opioid use disorder that needs to be treated.

CATR: Despite these new recommendations, have you found that methadone programs may still consider benzodiazepine found in urine toxicology a reason for discharge or at least decreasing the methadone dose?

Dr. Morford: We see that a lot. That is not a practice that I recommend, and most guidelines don't recommend that methadone doses should be tapered just based on the fact that someone is using a benzodiazepine (Food and Drug Administration, 2017; www.tinyurl.com/td648oq). When we see evidence of impairment, that's really the time to think about decreasing the dose of methadone to optimize safety, but it really shouldn't be done simply due to the presence of benzodiazepine metabolites in toxicology testing.

CATR: What do we know about treatment of patients with benzodiazepine use disorder?

Dr. Morford: Here, the recommendation is also to taper to discontinuation. We don't have great medications specifically to treat benzodiazepine use disorder, so typically it will require coming up with a patient-specific taper plan, depending on how risky the situation seems. If this is somebody we're really worried about having withdrawal seizures, then we might want to recommend an inpatient facility, but more often it can be done in outpatient settings. Tapering can be successful at a dose-reduction rate of about 5%–10% per week or month. Addition of an anticonvulsant, like gabapentin, can be considered for high-dose withdrawal. Switching to a longer-acting benzodiazepine (clonazepam, diazepam) may make for a more tolerable tapering experience.

CATR: Are there meds that you recommend to help patients during the time period they are tapering off benzodiazepines?

Dr. Morford: We can make the taper more tolerable by providing medications like hydroxyzine, clonidine, or trazodone to help people sleep and help with anxiety. These medications may be tapered over a period from several weeks to 6 months. The reality is that you're going to make progress on the taper as best you can, in partnership with the patient. (Editor's note: Also see *CATR,* May 2016 on benzodiazepine tapering, and *TCPR,* Jan 2019 on deprescribing.)

CATR: Any specific guidance on how to discuss tapering with patients?

Dr. Morford: When someone is coming and seeking help for benzodiazepine use disorder, they're seeking treatment because something about the benzodiazepine use has become problematic in their lives. So, we should use motivational interviewing strategies to reaffirm that their use has caused problems and make sure that, in addition to the formulation and plan, we provide education about the risks associated with benzodiazepines. I'm often surprised that patients who may know quite a bit about the harms of opioids may know less about the harms of benzodiazepines, so education is a key component at the outset of a taper. Frequent follow-up and expressing non-abandonment is important, too. When patients make an initial step in a taper, they sometimes notice they feel better, and this can be motivating.

CATR: Thank you for your time, Dr. Morford.

Research Updates

SMOKING

E-Cigarettes vs Nicotine Replacement for Smoking Cessation

REVIEW OF: Hajek P et al, *N Engl J Med* 2019;380(7):629–637

E-cigarettes are increasingly popular, often touted as exposing users to fewer toxins than combustible cigarettes. Might they be useful for smoking cessation and abstinence? To answer this question, Hajek et al performed a multicenter randomized controlled trial comparing e-cigarettes to nicotine-replacement therapy (NRT) in adults seeking help to quit smoking.

Participants were recruited through a smoking cessation program in the United Kingdom. Of the 2045 screened, 886 participants (median age 41 years, 51.8% male, average of 15 cigarettes per day) were enrolled in the study based on not having a strong preference for e-cigarettes or NRT and not currently using either product. They were then randomized to receive either an e-cigarette or NRT, and asked not to use the non-assigned product.

Those in the e-cigarette group were given an e-cigarette and bottle of tobacco-flavored e-liquid containing 18 mg/mL of nicotine, and directed to purchase their own future e-liquid. Those in the NRT group were offered their preferred product; most participants chose the patch combined with the gum.

At baseline, 4 weeks, and 1 year, participants completed trial visits in which carbon monoxide levels (a proxy for combustible cigarette consumption) were checked. Most participants (78.8%) completed the 1-year follow-up. Dropouts were classified as not being abstinent. The primary outcome measured was sustained abstinence at 1 year. Secondary outcomes included reported treatment usage, perceptions of assigned products, and respiratory symptoms.

Abstinence rates were higher in the e-cigarette group at all time points. The e-cigarette group achieved a 1-year abstinence rate of 18.0%, compared with 9.9% in the NRT group (RR 1.83, CI 1.30–2.58). Among all participants who did not achieve abstinence, those in the e-cigarette group also had higher rates of reduced smoking (RR 1.75, CI 1.12–2.72). The authors speculated that e-cigarettes were more effective because they better alleviated tobacco withdrawal and allowed for greater tailoring of treatment dose.

There was a higher rate of product usage in the e-cigarette group than in the NRT group: 39.5% and 4.3% at the end of the 1-year study period, respectively. This difference was even greater among participants with 1 year of abstinence (80% vs 9%). E-cigarettes were rated higher than nicotine replacement in terms of providing satisfaction and reducing urges to smoke.

Interestingly, regarding respiratory symptoms, the e-cigarette group had less cough and phlegm than the NRT group, and both groups were similar regarding incidence of wheezing and shortness of breath.

CATR'S TAKE

Smoking cessation remains difficult, as demonstrated by the low success rate in this study regardless of the treatments rendered. E-cigarettes may be more efficacious than NRT for abstinence in those motivated to quit smoking. Still, given the risks associated with e-cigarettes—including vaping-associated illnesses, inhaling potentially toxic aerosols, and the possibility of burns from vaporizer devices—clinicians should use caution in recommending e-cigarettes as treatment. Clinicians should also be mindful of the CDC's guidance, issued in February 2020, which states that patients choosing to use e-cigarettes for smoking cessation should completely switch from cigarettes to e-cigarettes and avoid an extended period of dual use. Further research is needed to compare e-cigarettes with other smoking cessation treatment modalities, including bupropion, varenicline, and behavioral treatments.

—C. Jason Mallo, DO. Dr. Mallo has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

COCAINE

Amphetamines and Topiramate for Cocaine Use Disorder

REVIEW OF: Levin FR et al, *Drug Alcohol Depend* 2020;206:107700

In 2017, an estimated 2.2 million Americans used cocaine, with about 966,000 of them meeting criteria for cocaine use disorder (CUD) (SAMHSA, 2018). Unfortunately, there are still no FDA-approved treatments for CUD. Amphetamines increase synaptic dopamine transmission and may therefore reduce the reinforcing properties of cocaine. Topiramate, an anticonvulsant that enhances gamma amino butyric acid (GABA) activity, can reduce cocaine-induced dopamine release and may modulate the reinforcing effects of co-administered amphetamines. Previously, a single-site study suggested that a combination of amphetamine and topiramate can reduce cocaine use in individuals with high baseline cocaine consumption (Mariani JJ et al, *Biol Psychiatry* 2012;72(11):950–956). Now, researchers have conducted a larger trial with the same combination, among people who use cocaine, across two large metropolitan areas.

This trial tested the combination of mixed amphetamine salts extended-release (MAS-ER) and topiramate vs placebo in double-blinded, randomized design. The study was conducted over a 12-week period and included 127 adults (96 men, ages 18–60) with CUD. Participants reported using cocaine for at least 9 days in the previous month. MAS-ER was titrated to a maximum dose of 60 mg/day, and topiramate was increased to a maximum dose of 100 mg twice/day. The primary outcome was the proportion of individuals who achieved 3 consecutive weeks of abstinence, as measured by urine toxicology and self-report. Funding was provided by the National Institute on Drug Abuse.

The proportion of participants achieving 3 weeks of abstinence was significantly larger in the treatment compared to the placebo group (14.1% vs 0.0%, p = 0.03) after controlling for other factors.

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Secondary analyses showed that the proportion of participants who achieved any 3 consecutive weeks of abstinence (but not necessarily end-of-study abstinence) was higher for those receiving MAS-ER and topiramate (21.9%) compared to placebo (6.3%). Cocaine cravings also were significantly less prevalent among the treatment group ($p < 0.001$). Dropouts were high in both study arms (34% in the treatment group, 41% in the placebo group). Dry mouth was the only adverse event significantly more common in the treatment group than the placebo arm (16% vs 5%). Among those receiving MAS-ER and topiramate, 20.3% were discontinued from the medications due to increased blood pressure and heart rate.

CATR'S TAKE

The combination of amphetamine and topiramate can increase abstinence and decrease cravings among those with CUD. However, cardiovascular side effects limit widespread use, and it remains unclear whether the combination of MAS-ER and topiramate outperforms either medication alone.

—Reban Aziz, MD. Dr Aziz has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

ALCOHOL

Does Baclofen Titrated to High Doses Reduce Alcohol Use?

REVIEW OF: Rigal L et al, *Addiction* 2019 Dec 13 [Epub ahead of print]

Baclofen is a muscle relaxant and anti-spasmodic that has been used off-label for treating alcohol use disorder for many years. The research base is mixed, with studies showing inconsistent efficacy and tolerability at different doses. In this latest randomized, placebo-controlled trial, baclofen doses were titrated individually to better clarify how to use the medication in treatment.

This study took place in 62 French primary care centers and included 320 patients who were randomized to receive either baclofen or a placebo for 12 months. Patients were included if they were "high-risk alcohol consumers," meaning > 40 g/day (~2.9 US standard drinks) for women and > 60 g/day (~4.3 US standard drinks) for men. No detoxification was required. Doses started at 15 mg/day in divided doses, and both the baclofen and placebo arms could increase their dose at monthly intervals up to 300 mg/day. Patients who got up to 300 mg but felt that their dose wasn't helping them were allowed to switch to open-label baclofen for the rest of the study—these switchers were considered treatment failures for the primary study analysis. No psychosocial intervention was offered.

The primary outcome was no or low-risk alcohol consumption during month 12 of the study. Low-risk consumption was defined as < 20 g/day (~1.4 US standard drinks) for women and < 40 g/day (~2.9 US standard drinks) for men. There were several secondary outcomes, including mean daily alcohol consumption, number of days of abstinence, number of heavy drinking days, and craving scale ratings.

For the primary outcome, baclofen was effective, with 57% of patients achieving no or low-risk alcohol consumption on baclofen vs 37% with placebo. However, when the open-label switchers were not presumed to have failed treatment unless they did (a secondary outcome), the difference became non-significant. The only secondary outcomes that were significantly in favor of baclofen were mean daily alcohol consumption and number of days of abstinence. The median maximum baclofen dose reached in the treatment arm was 180 mg/day.

Limitations included high rates of treatment non-adherence (59% in the baclofen group and 80% in the placebo group) and high rates of missing data.

Most adverse events like drowsiness were not significantly higher in baclofen vs placebo. However, the baclofen group included 7 deaths with 1 suicide (vs 3 deaths in the placebo group) and 3 manic episodes (none in the placebo group). The deaths were not thought to be related to the study medication by an independent committee.

CATR'S TAKE

Baclofen appears to be somewhat effective at reducing alcohol consumption among those with unhealthy alcohol use, though various methodological issues lessen our confidence in the data. High rates of non-adherence in this study may mean that other supportive interventions, such as manualized behavioral interventions, could benefit those prescribed baclofen for unhealthy alcohol use.

—Thomas Jordan, MD. Dr. Jordan has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

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Muscle Relaxants: Sedatives Often Under the Radar
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2017;19(4):788–792). Combining opioids, benzodiazepines, and carisoprodol is reported to potentiate euphoria and has been called the "Holy Trinity"; this combination is associated with respiratory depression and increases the risk of opioid overdose (we recommend watching the Netflix documentary series, *The Pharmacist,* for an eye-opening account of a pill mill that specialized in prescribing the Holy Trinity to people with opioid use disorder). Short-term use, lower opioid doses, and cyclobenzaprine are associated with less risk of overdose.

CATR VERDICT: Clinicians may prescribe muscle relaxants on a short-term basis (2–3 weeks) for acute spasticity and muscle pain, but evidence for efficacy in chronic pain management is lacking. Educate patients about the risks of sedation and overdose in combination with other sedating substances. Cyclobenzaprine or tizanidine appear safer, but tapering is recommended after longer-term use. Avoid carisoprodol due to its potential for misuse and look out for it on prescription drug monitoring programs.

Expert Interview—Gabapentin Misuse and Diversion
Continued from page 3

to 95% (Goodman CW and Brett AS, *JAMA Intern Med* 2019;179(5):695–701). So, there's a lot of it out in the public and it's easy to access. That's certainly part of the problem.

CATR: How should we monitor use?

Dr. Vickers-Smith: Unfortunately, most often, toxicology screens for gabapentin are not used. They just aren't requested, so that's something to consider in monitoring misuse of gabapentin. We simply don't understand fully the risks of gabapentin misuse and may be unaware when people are taking such high doses, beyond the recommended dosing range: People may be taking 4 or 5 pills, or 2,000 mg, at once (the maximum safely tolerated total daily dose of gabapentin is 3,600 mg). Also, we need to consider whether prescribing gabapentin is the best choice for an individual patient, because there has also been a review about gabapentinoids for non-cancer pain outside of their FDA-approved indications and there's limited evidence for their effectiveness (Goodman CW and Brett AS, 2019); better evidence exists for other indications, including post-herpetic neuralgia and diabetic neuropathy. Certainly, we don't want people's pain to go untreated. We want to do our best in treating pain, and prescribers are faced with finding alternatives to opioids. The CDC has recommended gabapentinoids as a first-line alternative to opioids for pain. This is not a sweeping statement. Instead, we should go case by case and consider whether gabapentin is really the best treatment we have available for this individual.

CATR: You've been mentioning gabapentin a lot. What about pregabalin—do the two confer similar risks?

Dr. Vickers-Smith: There's not as much out there about pregabalin misuse, just because it's been scheduled since nearly right after its market release. So, given what we've seen, people may report using pregabalin, but not to the same extent. If they're misusing it, it's likely not to the same extent as gabapentin.

CATR: For patients whom we suspect are misusing gabapentin, do we have effective treatments available?

Dr. Vickers-Smith: At this point, we don't. Because gabapentin is typically used with other substances, we don't see a lot of people seeking just treatment for gabapentin addiction, per se. They may also be using opioids, alcohol, or benzos, which may be a higher priority for the patient and the clinician. Gabapentin may, also, be appropriately prescribed for the management of alcohol use disorder. So there is a lot to tease out there, and how to manage the unhealthy use of gabapentin is certainly an area that we need to explore.

CATR: Thank you for your time, Dr. Vickers-Smith.

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ALCOHOL

Gabapentin for Alcohol Use Disorder, Redux

REVIEW OF: Anton RF et al, *JAMA Intern Med* 2020;180(5):1–9

Gabapentin has had mixed results in the treatment of alcohol use disorder (AUD), but it is clearly effective in the treatment of alcohol withdrawal syndrome (AWS). In this study, researchers tested whether gabapentin might be effective specifically in treating adults with AUD who also had a history of AWS.

The investigators conducted a 16-week randomized controlled trial comparing gabapentin to placebo. Ninety patients with AUD and a history of AWS were enrolled (44 in the gabapentin arm, 46 in the placebo arm). Here, AWS was defined as a self-reported history of withdrawal symptoms; however, those with a history of withdrawal seizures were excluded.

Participants were aged 18–70 (94% were white, 77% were men) and drank a mean of 86% of pre-treatment days, with 83% being heavy drinking days (defined as 5 or more drinks per day for men and 4 or more drinks per day for women). They were required to have been abstinent for 3 days prior to randomization. The study took place in an academic medical center and was sponsored by the National Institute on Alcohol Abuse and Alcoholism.

Gabapentin was started at 300 mg at bedtime and titrated over 5 days to 300 mg in the morning, 300 mg at noon, and 600 mg at bedtime. Patients in both groups received nine 20-minute medical management visits.

After 16 weeks, more gabapentin-treated individuals had no heavy drinking days compared with placebo (27% vs 9%, $p = 0.02$), with a number needed to treat (NNT) of 5.4. More gabapentin-treated patients also achieved total abstinence compared to placebo (18% vs 4%, $p = 0.04$), with an NNT of 6.2. The effect was more pronounced for patients with histories of more severe withdrawal. Among those who had reported less severe withdrawal, there was no difference between gabapentin and placebo. There was more dizziness reported in the gabapentin arm (57%) than in the placebo arm (33%; $p = 0.02$), but no serious adverse events were reported.

CATR'S TAKE

Gabapentin reduced heavy drinking days and promoted abstinence in patients with AUD who had withdrawal symptoms. However, the trial doesn't address the effect of gabapentin beyond 4 months of use, and concerns remain regarding gabapentin misuse, addiction, and interaction with other sedating substances.

—Reban Aziz, MD.

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These questions are intended as a study guide. Please complete the test online at www.carlataddictiontreatment.com. Learning objectives are listed on page 1.

1. Due to concerns for adverse events including next-morning impairment, the FDA updated its labeling for zolpidem and extended-release zolpidem in 2013 to suggest which doses? (LO #1)

   [ ] a. 12.5 mg nightly for women and 12.5 mg nightly for men (extended-release zolpidem)
   [ ] b. 10 mg nightly for women and 10 mg nightly for men (zolpidem)
   [ ] c. 5 mg nightly for women and 5–10 mg nightly for men (zolpidem)
   [ ] d. 5 mg nightly for women and 5–10 mg nightly for men (extended-release zolpidem)

2. Which class of medication was associated with 21% of opioid-related deaths in 2017? (LO #2)

   [ ] a. Benzodiazepines [ ] b. Muscle relaxants [ ] c. Gabapentinoids [ ] d. Barbiturates

3. Which muscle relaxant is known for lowering blood pressure and so should be used with caution in patients at risk for hypotension or bradycardia due to other medical conditions? (LO #3)

   [ ] a. Baclofen [ ] b. Cyclobenzaprine [ ] c. Quinine [ ] d. Tizanidine

4. In a trial of amphetamine combined with topiramate for the treatment of cocaine use disorder, what adverse effects led to 20% of those in the treatment arm being discontinued from the study drug? (LO #4)

   [ ] a. Dry mouth
   [ ] b. Suicidal thinking
   [ ] c. Increased blood pressure and/or heart rate
   [ ] d. Mania

5. From 2009 to 2011, zolpidem was implicated in what percentage of adult visits to the ED due to adverse drug events from psychiatric medications? (LO #1)

   [ ] a. 3% [ ] b. 9% [ ] c. 12% [ ] d. 25%

6. Psychiatrists, as a specialty, are responsible for 50% of visits involving benzodiazepine prescriptions. (LO #2)

   [ ] a. True [ ] b. False

7. Carisoprodol is metabolized in the liver to what sedating substance that used to be marketed under the brand name Miltown? (LO #3)

   [ ] a. Chlordiazepoxide [ ] b. Meprobamate [ ] c. Dantrolene [ ] d. Methocarbamol

8. Which of the following is a major limitation in a recent randomized trial of baclofen titrated to high doses for the treatment of alcohol use disorder? (LO #4)

   [ ] a. There was a high degree of non-adherence to the study drug and placebo
   [ ] b. The trial only included participants with "low-risk" drinking
   [ ] c. Only one alcohol-related outcome was measured
   [ ] d. The trial only included patients in inpatient addiction treatment settings

9. Among people with substance use disorders, approximately what percentage are thought to misuse gabapentin? (LO #2)

   [ ] a. 10% [ ] b. 20% [ ] c. 40% [ ] d. 80%

10. What percentage of patients prescribed opioids are also prescribed muscle relaxants? (LO #3)

    [ ] a. 1% [ ] b. 5% [ ] c. 8% [ ] d. 10%

11. In a trial of amphetamine combined with topiramate for the treatment of cocaine use disorder, 14% of those receiving the study drug achieved 3 consecutive weeks of abstinence. (LO #4)

    [ ] a. True [ ] b. False

12. Gabapentinoids are thought to increase the risk of opioid-related overdoses by what mechanism? (LO #2)

    [ ] a. Electrolyte imbalances
    [ ] b. CNS depression
    [ ] c. Decreasing the seizure threshold
    [ ] d. Vasoconstriction

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Note From the Editor-in-Chief

The expansion of telemedicine—which health systems had been slow to adopt and payers had been reluctant to reimburse for years—has zoomed ahead in recent weeks. Sure, it's not perfect: The video connections can be finicky, and learning new digital platforms can pose challenges for both patients and providers. But with this transition come enormous opportunities to meet patients where they are and minimize their barriers to care.

Lately, I've engaged patients in addiction treatment who were previously too fearful to make their symptoms known, or felt too branded to come to the clinic. Now that the opportunities have arrived, it's on us to develop and refine effective and safe ways to engage patients in addiction treatment via telemedicine. In our next issue (July/August), we'll address telemedicine as an approach to care for addiction treatment, and weigh the evidence for its use in various models. Good luck to you in your tele-endeavors, keep innovating, and please do share your ideas.

Regards,
Benjamin Oldfield, MD
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