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Chris Aiken, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month: **Depression**

Learning Objectives

After reading these articles, you should be able to:

1. Deliver a nutritional plan to patients with ADHD who prefer not to take medications.
2. Refine your clinical understanding of varieties of depression as well as treatment resistance.
3. Mitigate the potential harms from the rising trend of coprescribing benzodiazepines and stimulants.
4. Summarize some of the current research findings on psychiatric treatment.

A Diet for ADHD

Chris Aiken, MD. Editor-in-Chief, The Carlat Psychiatry Report.

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The authors have disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Bestselling books have promised a dietary cure for ADHD since 1975's *Why Your Child Is Hyperactive,* but separating the science from the snake oil is no easy task. In this article, we walk you through three nutritional approaches to ADHD: elimination diets, dietary supplements, and the heart-healthy DASH diet. All have some empiric support, and at least one of them is ready for practice.

Elimination diets

The first ADHD diet was proposed by Ben Feingold, a prominent allergist and author of the 1975 bestseller mentioned above. Feingold was trying to help patients who were allergic to salicylic acid

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A new study supports the Mediterranean-style DASH diet for ADHD.

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Dr. Ronald Pies shares a meaningful question to ask in a brief medication visit: "What keeps you going?"

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Prescribing benzodiazepines and stimulants together raises risks of addiction, neurotoxicity, cognitive problems, and car accidents.

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Dr. Charles DeBattista identifies courses of action when a patient hasn't recovered after two antidepressant trials.

Q&A With the Expert

Understanding the Varieties of Depression

Ronald W. Pies, MD

Professor Emeritus of Psychiatry and Lecturer on Bioethics and Humanities, SUNY Upstate Medical University; Clinical Professor of Psychiatry, Tufts University School of Medicine; Editor-in-Chief Emeritus, Psychiatric Times.

Dr. Pies, expert for this educational activity, has disclosed no relevant financial relationship(s) with ineligible companies to disclose.

TCPR: Is depression one illness or many?

Dr. Pies: I'd say many, or at least several. When psychiatrists use the term "depression," it's a bit like a car mechanic saying you have "engine trouble." It can mean many things, and it's not a very precise diagnosis. Depressions vary in their clinical presentation, polarity, and etiology.

TCPR: DSM-5 has a few specifiers to subdivide major depressive disorder (MDD). Which do you find most useful?

Dr. Pies: I make use of two DSM-5 specifiers: psychotic features and mixed features. My algorithm is pragmatic and risk based. When I first see a patient with major depression, my first diagnostic "cut" is whether they need emergency hospitalization, usually because of psychosis or high suicide risk. If not, I next want to know if the depression is best

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Expert Interview – Understanding the Varieties of Depression

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explained by some acute or comorbid medical-neurological or substance-related condition that needs immediate evaluation. For example, depression is one of the most frequent neuropsychiatric disturbances in acute stroke, seen in 6%–52% of acute stroke patients (Caeiro L et al, *J Psychiatry Neurosci* 2006;31(6):377–383). Next, I look at whether the episode has "mixed" hypomanic/manic features, which is a new specifier in DSM-5.

TCPR: Do you mean whether the patient has bipolar disorder?

Dr. Pies: That is only part of this specifier. In the past the DSM only recognized mixed features in bipolar depression, but about one in four patients who don't meet criteria for bipolar disorder have a few hypomanic/manic symptoms that overlap with their depression (Vázquez GH et al, *J Affect Disord* 2018;225:756–760). The frequent presence of mixed symptoms argues against a strictly dichotomous system of bipolar vs unipolar or mania vs depression. If we posit a continuum of mood disorders—from, say, recurrent major depressive episodes on the far left to clear-cut manic episodes on the far right—there are still treatment implications for depressed patients who have mixed or manic features.

TCPR: How so?

Dr. Pies: In general, for these folks, I try very hard to stay away from antidepressant treatment, and I try equally hard to make lithium—sometimes combined with an atypical antipsychotic or anticonvulsant—a part of their long-term treatment. Given its antisuicide effects, I think lithium is underutilized in this setting, but more controlled studies are needed (Sani G and Fiorillo A, *CNS Spectr* 2020;25(4):449–451).

"I always point out the need for more than medication, which is a bridge between feeling terrible and feeling better. But you still need to walk across that bridge. That's where psychotherapy comes in."

Ronald W. Pies, MD

TCPR: What are your top tips for distinguishing unipolar from bipolar depression?

Dr. Pies: I sometimes use the term "bipolaroid"—or, if you like, "bipolar-ish"—to describe patients whose syndromes lie somewhere on the right (toward the bipolar) side of the continuum I just described, but who lack a history of frank manic or hypomanic episodes. Some of the clues to this bipolaroid mood disorder include family history of bipolar disorder, psychomotor retardation during depression, and more abrupt onset and/or termination of depressive bouts. Anecdotally, some patients will report a brief burst of increased energy or subthreshold hypomanic symptoms immediately before bipolar depression onset. And one of the most useful clues pointing toward bipolar spectrum illness is the complaint that antidepressants make the patient feel worse even if they don't develop full mania on them—for example, the patient complains of feeling antsy, wired, agitated, or unable to sleep when taking antidepressants. Finally, psychotic features are more common in bipolar than in unipolar depression.

TCPR: DSM also distinguishes bipolar II from bipolar I depression. Do you see these differently?

Dr. Pies: Yes, to some extent. Across the lifespan, people with bipolar II disorder spend much more time in depression than those with bipolar I. Also, bipolar II depression has a lower susceptibility to antidepressant-induced switching into mania, compared with bipolar I—in other words, switch rates associated with antidepressant use are twice as high with bipolar I disorder vs bipolar II (Gitlin M and Malhi GS, *Int J Bipolar* 2020;8(1):5). One or two mood disorder specialists believe it is safe and effective to use antidepressant monotherapy—that is, without a mood stabilizer—as maintenance treatment in patients with bipolar II depression, but I think this is a minority viewpoint and it's not something I would recommend (Parker G, ed. *Bipolar II Disorder: Modelling, Measuring, and Managing*. 3rd ed. Cambridge University Press; 2019).

TCPR: Is depression ever *not* an illness?

Dr. Pies: Absolutely. We often attribute "depression" to people who are actually experiencing grief, demoralization, or despair. These are not "illnesses," but rather normal parts of the human condition under certain adverse circumstances. Grief, for example, is essentially an adaptive response to a major loss—some would even say that grief is what makes us truly human. Demoralization and despair have some symptomatic overlap with MDD, but they have distinct features that require careful differential diagnosis, since despair is associated with suicide risk and illicit substance use.

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Expert Interview – Understanding the Varieties of Depression
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TCPR: In 2013, the DSM removed the "bereavement exclusion" from depression. What do you think about this?
Dr. Pies: I think clinically depressed, bereaved patients benefitted from DSM-5 dropping the bereavement exclusion, in that they became more likely to be directed toward professional treatment (which does not necessarily mean medication). I don't buy the claim that removal of the bereavement exclusion "medicalized normality," because grief after death of a loved one does not "normally" present with the full panoply of MDD signs and symptoms.
TCPR: What's your opinion on prolonged grief disorder?
Dr. Pies: This was added in the 2022 DSM-5 Text Revision, and I would say roughly the same thing about it as I would about removing the bereavement exclusion. However, I had advocated that the new diagnosis be called "prolonged *dysfunctional* grief disorder," because if you read the criteria, these folks are quite seriously impaired and dysfunctional. I think the APA underestimated the negative reaction the term "prolonged grief disorder" would provoke among the general public, and even among many experienced psychiatrists, who rightly argue that grief doesn't have an expiration date. That's very true—but people with prolonged grief disorder are really suffering, and they'd benefit from better recognition and treatment. Dr. Katherine Shear helped develop a specific psychotherapy for this disorder, complicated grief treatment, and it proved more effective than a more traditional model of grief therapy, interpersonal psychotherapy, in two head-to-head trials (Shear K et al, *JAMA* 2005;293(21):2601–2608; Shear MK et al, *JAMA Psychiatry* 2014;71(11):1287–1295).
TCPR: How do you tell the difference between clinical depression and normal grief?
Dr. Pies: Folks with "normal" grief often experience a mixture of sadness and more pleasant emotions as they remember the deceased. Their anguish and pain are usually experienced in waves or pangs rather than continuously, the latter usually being the case in major depression. The grieving person typically maintains the hope that things will get better. In contrast, the clinically depressed person's mood is almost uniformly one of gloom, despair, and hopelessness—nearly all day, nearly every day. And, unlike the typical bereaved person, the individual with major depression is usually quite impaired in terms of daily functioning. Furthermore, with grief, the person's self-esteem usually remains intact. In major depression, feelings of worthlessness and self-loathing are very common. In ambiguous cases, a patient's history of previous depressive bouts, or a strong family history of mood disorders, may help clinch the diagnosis.
TCPR: Is medication alone ever appropriate for depression?
Dr. Pies: Very rarely. I believe that some form of "talk therapy" is always appropriate for patients who are clinically depressed. That doesn't mean psychoanalysis or long-term psychotherapy is needed. Sometimes a few sessions of supportive therapy or cognitive behavioral therapy will suffice. Virtually all depressive syndromes have a psychosocial component, and sometimes a cultural or spiritual one as well. That component may not be causal—in fact, disturbances in the psychosocial realm may be secondary to the depression itself—but it almost always merits attention.
TCPR: Do some depressions need psychotherapy more than others?
Dr. Pies: Well, some depressions are more responsive to psychotherapy, and milder depressions may respond to psychotherapy alone, so it is worth trying as an initial approach. But when it comes to "needing" psychotherapy, the answer is very different. The case for psychotherapy becomes very strong when prominent psychopathology is present—for example, chronic difficulty in interpersonal relationships, pronounced cognitive distortions, or chronically low self-esteem.
TCPR: What do patients need to know about depression?
Dr. Pies: I'll start by saying what we should *not* be telling patients—namely, that their depression is "caused by a chemical imbalance in the brain." Now, of course, that doesn't mean biology isn't heavily involved in clinically significant depression—it certainly is! In my own practice, I draw an old-fashioned funnel and show three "inputs" to the funnel: "biological," "psychological," and "social." At the bottom of the funnel, I write "depression." If a patient is curious about the biological component, I will sometimes provide an appropriate article or talk a bit about genetic influences, nerve growth factors like BDNF, serotonin, etc. I will point out that what we call "major depression" is most likely a group of related conditions, probably with differing etiologies. I discuss the risks and benefits of medications, and I always point out the need for more than medication. "Medication is a bridge between feeling terrible and feeling better," I tell patients, "but you still need to walk across that bridge." That's where psychotherapy comes in.
TCPR: Any tips for humanizing a brief medication visit?
Dr. Pies: That's a big ask! To borrow a phrase from the literature on borderline personality disorder, sometimes "it's not the words, it's the music." Our eye contact; our tone of voice; a gentle, empathic pat on the shoulder (when appropriate)—all these things can help humanize those hurried and harried med-check meetings. Here's a question I learned from Dr. H. Steven Moffic that I've found helpful in gaining an understanding of the patient during a brief visit: "What keeps you going?"
TCPR: Dr. Pies, what has kept *you* going?
Dr. Pies: Many factors might discourage me from psychiatry if I were entering the field today: the paperwork; third-party payer hassles; limited access to services; staffing shortages; and, sadly, a lot of misunderstanding and animus directed at psychiatry from the general public. But psychiatry is still a great and noble profession, with almost endless possibilities for creative work. As one of my mentors, Dr. Robert Daly, used to quip, "In psychiatry, you can do biology in the morning and theology in the afternoon." I have found that to be true—and I think that is what has always kept me going.
TCPR: Thank you for your time, Dr. Pies.

A Diet for ADHD

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(aspirin) by having them eliminate salicylate-rich foods, including tomatoes, cucumbers, and oranges, as well as artificial food colorings that resembled salicylate. In the process, he noticed that his patients with comorbid ADHD experienced a full remission of the psychiatric syndrome.

Feingold's diet was tested in over a dozen small controlled trials of ADHD, but the results were mixed and a meta-analysis came up negative. However, studies that focused on eliminating artificial colors were generally positive, yielding a small effect size (0.28) across 15 small, double-blind crossover trials that tested children on and off this elimination approach (Schab DW and Trinh NHT, *J Dev Behav Pediatr* 2004;25(6):423–434).

Later studies found that artificial colorings could cause ADHD symptoms in children without ADHD. Those studies also added sodium benzoate to the list (a preservative and flavor enhancer found in packaged sauces, snacks, and sodas). In response, several countries banned food colorings and the European Union placed warnings on foods containing them (Rytter MJH et al, *Nord J Psychiatry* 2015;69(1):1–18). Although Feingold hypothesized that this was an allergic phenomenon, these additives also have pharmacologic-like mechanisms, inhibiting enzymes involved in the metabolism of dopamine and norepinephrine (Eagle K, *Physiol Behav* 2014;135:174–179).

Circling back to the allergy theory, several studies tested the effects of allergy-inducing foods like dairy, wheat, eggs, chocolates, nuts, and citrus fruits on ADHD. This approach found support in three small, blinded crossover trials where children eliminated the food for two to three weeks and then reintroduced either the original food or a placebo food. A similar on/off approach is sometimes used to test these foods in practice. If the food is causative, symptoms usually return within a few hours to a few days of its reintroduction (Stevens LJ et al, *Clin Pediatr (Phila)* 2011;50(4):279–293).

Other research has linked ADHD to chemicals that leach into foods from cans and plastic containers, but these associations are limited to epidemiologic and animal studies. A controlled trial in humans would be unethical because these chemicals, which include bisphenol A (BPA), phthalates, and phenols, have neurotoxic, carcinogenic, and endocrine-disrupting effects (Moore S et al, *Int J Environ Res Public Health* 2022;19(5):2849).

In summary, artificial colorings, sodium benzoate, and chemicals like BPA are best avoided as they can worsen cognition in anyone. Allergy-inducing foods, in contrast, are probably only relevant to patients with food allergies, and identifying those patients is difficult and time-consuming.

Best Nutritional Practices for ADHD

Food	Daily Servings	Examples
Vegetables	4–5	• Fresh, frozen, raw, and cooked all work • Berries and dark green vegetables have particular brain benefits
Fruits	2–3	
Whole grains	2–3	• Steel cut oats, brown rice, quinoa, spelt, barley, rye, amaranth, farro • Unprocessed sources are preferred; otherwise, select products labeled "100% whole grain"
Lean meats	<6	• Wild fresh, frozen, or canned seafood • Free-range poultry, pastured lamb, and grass-fed beef are suggested • Eggs count (1 egg = 1 serving)
Nuts and seeds	2–3	• Low-salt nuts are preferred • Nut butters are fine, but aim for those that are low in sugar, salts, and preservatives
Beans	1–2	• Lentils, chickpeas, black beans
Dairy	2–3	• Plain unsweetened yogurt; cheeses (Swiss, feta, and Parmesan are best)
Fats and oils	2–3	• Extra-virgin olive oil is preferred for brain and heart health

Foods to Avoid

- Sweets, sodas, added sugars, refined grains
- Fried, fast, packaged, or processed food
- Hot dogs, bacon, sausage, and deli meats
- Artificial dyes or colorings, sodium benzoate, and BPA (minimize canned foods and drinks, use BPA-free plastics, and do not microwave in plastics)

Supplementation

Children with ADHD are more likely to have low levels of iron, magnesium, omega-3 fatty acids (fish oil), and zinc, but can supplementation with these nutrients improve ADHD? Most of the investigations into this area suffer from poor designs and inconsistent results, but meta-analyses did find a small benefit when omega-3 fatty acids (12 trials, total n=735) and zinc (seven trials, total n=727) were used to augment stimulant medications (Bloch MH and Qawasmi A, *J Am Acad Child Adolesc Psychiatry* 2011;50(10):991–1000).

Omega-3 fatty acids come in two forms—docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)—and most of the positive trials used higher amounts of EPA, around 600 mg/day. We saw a similar pattern in depression, where only the trials with a high ratio of EPA:DHA (at least 2:1) trended positive.

The typical dose in the zinc studies was 15 mg/day of zinc gluconate, glycinate, or sulfate. These studies may not apply in the US, however, where only 12% of the population is deficient in zinc. The only US trial of zinc was negative, while the positive trials were carried out in countries where nearly half the population is deficient in zinc: Chile, Iran, and Turkey (Granero R et al, *Nutrients* 2021;13(11):4059).

A heart-healthy diet

Zinc deficiency may be rare in the US, but the Western diet is pervasive here, with its heavily processed foods that are rich in simple sugars, salt, and unhealthy fats. The Western diet is associated with diabetes, heart disease, depression, and age-related cognitive decline, and a 2011 study added ADHD to that list. This study

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followed a cohort of 2,868 Australian children from birth to age 14. Those raised on a Western diet were 2.2 times more likely to develop ADHD (Howard AL et al, *J Atten Disord* 2011;15(5):403–411).

The Australian study adjusted for confounding variables like physical activity, caloric intake, and the educational and financial status of the parents, but it could not rule out the possibility that children with ADHD are simply more likely to eat unhealthy foods. That explanation was addressed last year in a randomized trial that tested the heart-healthy Dietary Approaches to Stop Hypertension (DASH) diet in 80 Iranian children with ADHD who were not taking medication (Khoshbakht Y et al, *Eur J Nutr* 2021;60(7):3647–3658).

The DASH diet was developed for hypertension, but the foods it emphasizes are also associated with lower rates of ADHD in epidemiologic studies: fruits, vegetables, fish, whole grains, nuts, and beans. It is also low in food dyes, additives, and the hallmarks of the Western diet: sugar, salt, saturated fats, cholesterol, and refined grains. The children were randomized to the DASH diet or a control diet that was similar enough in its rigor and caloric requirements to pass as a blinded placebo. Compared to controls, those on the DASH diet had significant improvements on multiple parent-, teacher-, and child-rated measures of ADHD after three months. They also had more prosocial behaviors and fewer conduct problems.

A nutritional plan

Fifty years of research has brought three dietary approaches to ADHD, so where to begin? The DASH diet has several advantages. It is risk-free, easy to implement, and has numerous health benefits. It is also likely to translate to the adult population. The DASH diet was associated with cognitive benefits in epidemiologic studies of adults and is similar to the Mediterranean-style diet that improved adult depression in several controlled trials (van den Brink AC et al, *Adv Nutr* 2019;10(6):1040–1065). We've blended the DASH diet along with foods to avoid in ADHD (artificial colors, sodium benzoate, and BPA) in the patient-friendly table on page 4.

This diet delivers plenty of omega-3s, but dietary sources are usually low in the EPA fatty acids needed for mood and ADHD, so supplementation may still be beneficial (see *The Carlat Psychiatry Report* March 2022 for EPA-rich products). Minerals like zinc may help when there is a deficiency, and avoiding allergy-inducing foods may help when the patient has an identified allergy.

CARLAT VERDICT

Ask your patients with ADHD about their diet. If it's heavy in sugar, salt, unhealthy fats, processed foods, and artificial colors, suggest a three-month trial of the DASH diet, and rate their symptoms before and after the trial.

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The Benzodiazepine-Stimulant Combo: What Could Go Wrong?

Chris Aiken, MD. Editor-in-Chief, The Carlat Psychiatry Report. *Practicing psychiatrist, Winston-Salem, NC.*

Dr. Aiken, author of this educational activity, has no relevant financial relationship(s) with ineligible companies to disclose.

Benzodiazepines and stimulants are best avoided in combination, but even if you don't prescribe them together, you'll probably have to manage the combo as you take over the care of new patients. Use of this combination is on the rise. In 2018, around one in 15 patients who were prescribed a benzo were also prescribed a stimulant, an increase of 40% over 2013. The alprazolam-amphetamine combo is the most common, and affluent, working-age adults are the most likely to receive it (Borrelli EP et al, *J Manag Care Spec Pharm* 2022;28(1):58–68). Most (60%) of these combinations come from primary care, but psychiatrists are responsible for another 30%.

There are no clinical trials on this combined treatment, but I'll offer some guidance here from my own experience and research in animals, healthy subjects, and patients with substance use disorders. The first step is to understand why the patient is taking these medications. There are a few possibilities, but only one calls for rapid discontinuation of the drugs: prescription medication use disorder.

Substance use disorders

Prescription misuse may not be apparent on the first interview, but it will usually become clear with time. Contact the patient's past prescriber and check for evidence of doctor shopping in your state's prescription monitoring system. If you continue the combination, a random drug screen can clarify if the patient is not taking—and possibly diverting—the medications, or if they are using the meds along with other drugs of abuse. Watch out for opioids, as both stimulants and benzos increase the risk of opioid abuse and overdose.

Benzos enhance the opioid high but actually dampen the rewarding effects of stimulants (Lile JA et al, *Drug Alcohol Depend* 2011;119(3):187–193). That is particularly true with oxazepam, which is unique among the benzos for its ability to raise neurosteroids that block the rewarding properties of drugs of abuse (Spence AL et al, *Drug Alcohol Depend* 2016;166:209–217). Oxazepam also has a lower abuse liability than most benzodiazepines when used on its own.

On the other hand, amphetamines can lead to benzodiazepine abuse, as patients often turn to benzodiazepines to ease anxiety and other undesirable effects of amphetamines (Darke S et al, *Addiction* 1994;89(12):1683–1690). That pattern also shows up in practice when clinicians prescribe one drug to manage the side effects of the other.

Chasing side effects

Some patients end up on the two medications to manage side effects. Benzos

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The Benzodiazepine-Stimulant Combo: What Could Go Wrong?
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relieve anxiety and insomnia from stimulants, and stimulants relieve cognitive and motivational problems from benzos. The problem is that the relief is temporary and adds further risks to the picture. In these cases, the clinician's goal is to taper the patient off the drug that caused the side effect and—if needed—replace it with another. For example, if amphetamine caused anxiety, a trial of methylphenidate or a nonstimulant for ADHD may provide relief.

When insomnia is the problem, behavioral approaches are the first-line treatment. Benzodiazepines have not been studied for insomnia in ADHD*, but surprisingly the related hypnotics zolpidem and eszopiclone both failed in controlled trials of this population. Melatonin actually has more solid evidence in ADHD, perhaps because it addresses the "night owl" syndrome that is more common in ADHD (Barrett JR et al, *J Child Adolesc Psychopharmacol* 2013;23(10):640–647). Another approach is to augment or switch to an alpha-agonist like clonidine or guanfacine, both of which have sedative effects and are FDA approved in ADHD.

Insomnia causes ADHD-like symptoms even in people who do not have ADHD, and that can set off a vicious cycle of stimulants and sedatives, which illustrates the third reason that patients end up on this combination.

*Prior to 1994, only the hyperactive form of ADHD was recognized. Several controlled trials from the 1960s tested benzodiazepines for this "hyperkinetic syndrome" as it was called, but their use fell out of favor due to their cognitive effects and abuse potential.

Lifestyle medication

Some patients on a benzo-stimulant combo do not have a psychiatric diagnosis and instead are taking the drugs to improve their performance at work. Often the problem starts with work stress, which worsens sleep, and that in turn worsens work performance. Stimulants reverse some of the cognitive effects of sleep deprivation, but they do so at a price. In one study of healthy adults, cognitive performance improved after taking a stimulant, but then was worse the next day because the drug disrupted sleep (Tselha T et al, *Behav Brain Res* 2019;370:111940). In these situations, I recommend behavioral approaches to sleep and cognition, including cognitive behavioral therapy for insomnia, aerobic exercise (30 minutes/day), and a Mediterranean-style diet. I'll also emphasize the neurotoxic potential of benzos and stimulants, a problem that is amplified when the two are used together (Dutt M et al, *Physiol Behav* 2020;222:112935).

Complex, treatment-resistant disorders

Physicians often resort to symptomatic treatments when evidence-based therapies fail. This approach can quickly lead to a benzo-stimulant combo in hopes of addressing energy, concentration, sleep, and anxiety. In these patients, careful questioning may reveal a diagnosis that was never treated, such as bipolar disorder, PTSD, or panic disorder. Short of that, the options are limited because these patients have usually tried reasonable alternatives. In this situation, there is generally no urgent need to taper the off-label drugs. Rather, the concern is that the patient will develop tolerance to any benefits brought by the benzo-stimulant combo, and that the two drugs may even cancel each other's therapeutic effects.

Benzodiazepines impair attention, memory, and processing speed (Crowe SF and Stranks EK, *Arch Clin Neuropsychol* 2018;33(7):901–911). Those effects are only partially reversed by stimulants, and when it comes to motor vehicle accidents the two seem to worsen each other's risks in a synergistic way. Both amphetamines and benzodiazepines raise the risk of car accidents, and when used in combination they are responsible for more car accidents than any other drug of abuse (Zarkowski PA, *Int J Psychiatry Med* 2020;55(2):82–104). Stimulants do improve driving performance when used in ADHD, but not in healthy adults, and the improvements are much more robust with methylphenidate than the amphetamines (Jerome L, *J Can Acad Child Adolesc Psychiatry* 2006;15(3):105–125).

Rational use

In some situations, a stimulant-benzo combination is defensible even if not ideal, particularly if the benzo is used sparingly (no more than once per week) such as for panic disorder or a simple phobia. That level of use probably poses no greater threat than drinking an occasional glass of wine while taking a stimulant for ADHD.

Tapering

Each of these five scenarios requires a different approach. One allows continuation (rational use) and one requires discontinuation (overuse). For the other three, a gradual taper is in order. In the latter cases, as long as the drugs are not being misused, the combo poses no imminent threat, but it does carry long-term risks of tolerance, insomnia, traffic accidents, and cognitive problems. Tapering is difficult and works best when the patient trusts the clinician, understands the rationale, and is in a relatively stable condition. Explain that you cannot prescribe the combination long term and work out a collaborative plan regarding which to taper first. Both drugs have withdrawal syndromes, but stimulant withdrawal is usually the milder of the two, consisting of fatigue or depression.

The general principle of a taper is to go faster at first (eg, lowering a benzodiazepine every two to six weeks) and slower when you get to the lower dose range (lowering every two to three months). Stimulants can usually be tapered faster, such as over one to three months. Longer tapers may be necessary if the patient has been on the combo for many years. If the taper is difficult, allow the patient to slow down the rate, but avoid going back up to a previous dose.

CARLAT VERDICT

When taking over the care of a patient on a benzo-stimulant combination, don't rush to stop the meds unless they are clearly being abused. Instead, try to understand the problems that brought them to this combination, search for better ways to address them, and work collaboratively on a gradual taper.

Q&A With the Expert

Treatment-Resistant Depression

Charles DeBattista, MD

Professor of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA.

Dr. DeBattista has reported receiving research funding from pharmaceutical companies. This article was reviewed by Dr. Aiken, Editor-in-Chief, who has concluded that there is no evidence of commercial bias in this educational activity.

TCPR: What is your approach to treatment-resistant depression (TRD)?

Dr. DeBattista: The first step is a good history. Were the trials adequate in dose and duration? How well were they tolerated? What symptoms most bother the patient, and how did they evolve over time?

TCPR: What does the course tell us?

Dr. DeBattista: Most depressions have a gradual onset and offset, but when the episodes cycle frequently or begin and end abruptly, particularly with an onset before the age of 25, it may be a sign of bipolar disorder. Even if they don't meet full criteria for bipolar disorder, I will look for bipolar spectrum features as these are common in treatment resistance. Patients may have mixed-manic symptoms during the depression, or brief hypomanias that are shorter than the required four-day duration. Psychotic features also raise the risk of treatment resistance, as do comorbidities: substance use, personality disorders, OCD, a history of childhood trauma, and medical disorders (Nemeroff CB et al, *Proc Natl Acad Sci U S A* 2003;100(24):14293–14296).

TCPR: Which medical disorders do you look for?

Dr. DeBattista: There's a long list of them, but most are more contributory than causative: cardiovascular and metabolic disease, stroke, obstructive sleep apnea, and inflammatory illnesses like cancer, arthritis, or recent infections including COVID-19. It's relatively rare that we have a eureka moment in the medical workup, but sometimes we find an endocrine cause like hypothyroidism, Cushing's or Addison's disease, or hypogonadism in men.

TCPR: Do you mean low testosterone?

Dr. DeBattista: I'm not talking about the normal decline in testosterone that occurs with age. Testosterone supplementation is controversial there because it may raise the risk of heart attacks and stroke. But when the levels are one or two standard deviations off from the age-adjusted norms, a urology or endocrine consult may be helpful. Also, menopause increases the risk of depression in women, and estrogen can be helpful there (see *The Carlat Psychiatry Report* October 2020 for estrogen risks and dosing).

"Bupropion or modafinil augmentation may be appropriate for someone with low energy and drive. Pramipexole may be helpful for anhedonia. A second-generation antipsychotic may be better for someone who is agitated or has a lot of ruminations or trouble sleeping."

Charles DeBattista, MD

TCPR: What do you do when a patient hasn't recovered after two antidepressant trials?

Dr. DeBattista: You can augment, switch to an antidepressant from a class they have not tried yet, or use an intervention like transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), or the ketamines. Some forms of intensive psychotherapy also have evidence, as does aerobic exercise. In terms of medication, augmentation is generally faster and more effective than switching, and the options include second-generation antipsychotics, thyroid, lithium, bupropion, the modafinils, or a dopamine agonist like pramipexole (Nuñez NA et al, *J Affect Disord* 2022;302:385–400).

TCPR: How do you choose the augmentation agent?

Dr. DeBattista: It depends on the patient's treatment history and which symptoms are most prominent. Bupropion or modafinil augmentation may be appropriate for someone with low energy and drive. Pramipexole may be helpful for anhedonia. A second-generation antipsychotic may be better for someone who is agitated or has a lot of ruminations or trouble sleeping. For someone who's struggling with suicidal thoughts, lithium and ketamine or esketamine might be good choices.

TCPR: What would make you lean toward thyroid augmentation?

Dr. DeBattista: There's some evidence that it works better in women. I tend to consider it for middle-aged women with prominent fatigue, particularly if they have evidence of subclinical hypothyroidism in their labs or elevated antithyroid antibodies (Altshuler LL et al, *Am J Psychiatry* 2001;158(10):1617–1622).

TCPR: Do you use T3 (liothyronine, Cytomel) or T4 (levothyroxine, Synthroid)?

Dr. DeBattista: Most studies used T3, but either can work. One study compared them head-to-head and found greater benefit with T3, but it was a brief study (three weeks), and T4 may take longer to work because it has a half-life of five to seven days compared to the one-day half-life of T3 (Joffe RT and Singer W, *Psychiatry Res* 1990;32(3):241–251). I usually

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Expert Interview – Treatment-Resistant Depression
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start with T3 12.5 mcg/day and titrate to 25–50 mcg/day. The treatment is fairly well tolerated, and side effects like anxiety, tachycardia, and sweating usually improve with dose reduction. With long-term use, there is a concern that osteoporosis can develop, but this has not shown up in the clinical studies and is not a reason to avoid the treatment if the depression is significant. *(Editor's note: See the April 2022 issue of* The Carlat Psychiatry Report *for more information on thyroid dosing.)*

TCPR: Do you dose thyroid by symptoms, labs, or both?

Dr. DeBattista: Both. I check their TSH at baseline and again six to eight weeks later, and I prefer if it doesn't go to zero. A reasonable target for a TSH level is about 1.0. But at the same time, I'm also looking at whether the patient is getting some relief from their core symptoms.

TCPR: Which antipsychotics work in TRD?

Dr. DeBattista: Some are FDA approved for augmentation: aripiprazole (5–12.5 mg/day), brexpiprazole (2–3 mg), olanzapine (6–12 mg, FDA approved in conjunction with fluoxetine 25–50 mg/day), and quetiapine (150–300 mg). Cariprazine (1.5 mg/day) and risperidone (0.25–2 mg) have good evidence from randomized controlled augmentation trials but are not FDA approved. The challenge with the antipsychotics is that—with the possible exception of quetiapine—there aren't good long-term studies with any of them in depression (Liebowitz M et al, *Depress Anxiety* 2010;27(10):964–976).

TCPR: Most of their serious risks rise over the long term, like metabolic problems and tardive dyskinesia. How long do you continue antipsychotic augmentation?

Dr. DeBattista: I think it's reasonable to try to taper off after six to 12 months of recovery. I'm basing that on the time frame we need to continue an antidepressant after recovery, as this question has not been adequately studied with antipsychotics.

TCPR: Do you find pharmacogenetic testing useful in TRD?

Dr. DeBattista: Several large trials have looked at outcomes with pharmacogenomic-guided treatment, and the results have been mixed, but I think pharmacogenetic testing does have a limited role. For example, the genes that tell us about enzymatic activity in the liver can predict whether some medication levels will go too high, causing side effects, or too low, rendering them ineffective. Many psychiatric medications are metabolized by CYP2C19 and 2D6, like most tricyclics and some SSRIs and SNRIs, so those genes can be informative. A rapid metabolizer at those enzymes may never reach a therapeutic dose, while poor metabolizers may not tolerate the medication or—in the case of tricyclics and citalopram—may develop dangerous arrhythmias with high levels of the drug.

TCPR: Can you tell us more?

Dr. DeBattista: Other genetic tests look at pharmacodynamic markers of response, such as the short allele of the serotonin transporter gene, but it's not as clear that those genes are useful in predicting response. On the other hand, testing for the B-1502 haplotype in carbamazepine-treated patients is highly recommended as that haplotype is significantly associated with an increased risk of developing Stevens-Johnson syndrome, particularly in individuals of Han Chinese descent.

TCPR: Is TMS useful for TRD, or does it only work after one antidepressant failure?

Dr. DeBattista: The original TMS device (NeuroStar) was approved and indicated for depressed patients who had failed at least one but not more than four antidepressants. However, another TMS device (BrainsWay) did gain FDA approval in 2013 for true TRD (two antidepressant failures). Still, it wasn't until recently that I started to consider TMS for the more severe treatment-resistant cases where historically we'd consider ECT. TMS, like virtually all treatments, works better in less treatment-resistant patients. Our neuromodulation group at Stanford, under the leadership of Nolan Williams, developed an accelerated, five-day protocol that brought remission rates into the 70%–90% range for TRD, and the FDA cleared this "SAINT" protocol last September (see sidebar). Since such a high level of response is almost unheard of in a very resistant population, it will be important to verify these results with independent studies.

TCPR: When should we use the ketamines?

Dr. DeBattista: Their main benefit is that they can quickly reduce suicidality, potentially saving a patient from hospitalization. These drugs—particularly ketamine—have a large effect size in the short term, but they don't work as well in the long term (Lima TM et al, *Eur J Clin Pharmacol* 2022;78(3):311–338). Some patients develop habituation or tolerance. That's what we see clinically, and there are reports of tolerance when ketamine is used for pain management or anesthesia, although in most of that literature the drug was used in a higher dose range.

TCPR: Is there a subset that responds over the long term?

Dr. DeBattista: It's hard to say as the long-term esketamine trials were not controlled, but some patients swear by it. Typically, it is dosed every one to four weeks when used for maintenance—usually closer to every one to two weeks because the benefits tend to wear off after five to seven days, at least in the ketamine studies.

TCPR: Who is not a good candidate for the ketamines?

Dr. DeBattista: Patients who have a history of psychosis or substance use may not be the best candidates. Ketamine is a PCP derivative, so it can cause psychosis and there are concerns about its abuse potential. Recently I've become more careful about patients with a significant trauma history. Ketamine has small studies in PTSD, but we've also seen it trigger traumatic reactions: panic, dissociation.

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TCPR: Are there any other risks with the ketamines?

Dr. DeBattista: Cystitis and ulcerations in the bladder are common with ketamine abuse, but we haven't seen that with the lower doses that are used for depression. Acutely, patients can experience nausea as well as increases in heart rate and blood pressure, but these are rarely problematic at the doses used. These drugs are also cumbersome, requiring deliveries from specialty pharmacies and blood pressure monitoring during treatment. Patients have to be driven to and from the appointments and hang around the clinic for about two hours afterwards.

TCPR: You mentioned that we don't have good support for the long-term use of antipsychotics and ketamines. But in practice it can be hard to stop a treatment after it works.

Dr. DeBattista: We all get complacent about that, but it's important to have an end point in mind when you start a medication and set those expectations up early. With antipsychotics, you have to reassess for side effects and talk about tapering off if the benefit is no longer worth the risk. With the ketamines, if the patient hasn't responded within two weeks, we will stop the medication—but if they do respond, the path is less clear. Some of my colleagues continue it indefinitely, but I prefer to tell the patient that we are going to periodically reassess whether it is worth continuing. That depends on their response—are they maintaining a functional recovery or is tolerance developing? It also depends on adverse effects.

TCPR: There are other options with preliminary evidence in TRD: amantadine, celecoxib, minocycline. Where do these fit?

Dr. DeBattista: Among those "off the beaten path" options, the ones I've found most helpful have been dopamine agonists like pramipexole, and I would include amantadine in that group although it also affects glutamate transmission. We don't have much evidence for these, but they may be worth trying in patients who have not responded to multiple trials.

TCPR: A lot of trials focused on patients with *mild* treatment resistance—patients who failed only two antidepressants or sometimes just failed one. What can we do for those with four or more failures?

Dr. DeBattista: The success rate drops off substantially after several failed medication trials, not just the success rate for medications but also for interventions like ketamine, TMS, and ECT. In the best-case scenario—psychotic depression with no past trials—ECT may have a 90% remission rate in first-episode severe depression, but that may drop to 50%–60% after multiple medication failures. The trials on vagal nerve stimulation (VNS) and deep brain stimulation (DBS) involved more highly resistant depression, but those treatments have ultimately been somewhat disappointing. DBS was not FDA approved for depression because the large registration trials failed. VNS is FDA approved, and though the response rates looked rather low at first (around 30%), they look much better (40%–50%) in the latest studies that include five-year follow-up (Aaronson ST et al, *Am J Psychiatry* 2017;174(7):640–648).

TCPR: Is VNS a viable option?

Dr. DeBattista: For some. However, many will not respond, surgery is required to implant the device, and those wires are difficult to remove once placed. It also may take a year or two to see the full benefits. We don't have many takers, actually, but we do have patients in our clinics who have been implanted for a while and have done well.

TCPR: Any tips for working with the psychology of TRD?

Dr. DeBattista: I think one of the biggest challenges for clinicians is falling into the nihilism that many patients with TRD feel. They often become convinced that nothing is going to help, and you can become convinced as well. One of the most important things we offer is hope, and I've found there is always something else to try.

TCPR: I still have yet to try d-cycloserine.

Dr. DeBattista: I have actually never tried it either, though it did work in a small controlled trial (Heresco-Levy U et al, *Int J Neuropsychopharmacol* 2013;16(3):501–506). I have one patient who has tried everything and may be a d-cycloserine candidate.

TCPR: Thank you for your time, Dr. DeBattista.

SAINT: An Accelerated TMS

Researchers at Stanford University have developed a new way to deliver transcranial magnetic stimulation (TMS) with reports of impressive recoveries in treatment-resistant depression (TRD). SAINT is a high-dose, fast-paced TMS, delivering 10 treatments a day over one week (five days), compared to the usual one treatment a day over six weeks.

Early studies of SAINT reported unusually high remission rates in TRD: 70%–90%, higher than the 35% remission rates seen with traditional TMS. Those numbers were recently confirmed by a controlled trial, where SAINT brought 79% of patients to remission, compared to 13% with a sham protocol that was indistinguishable from SAINT (the blind was maintained). The benefits were largely maintained, albeit with mild slippage at one-month follow-up (Cole EJ et al, *Am J Psychiatry* 2022;179(2):132–141).

SAINT differs from traditional TMS in other ways as well. It uses rapid "theta burst" stimulation, a commercially available form of TMS that delivers the treatment in three minutes as opposed to the usual 20–40 minutes. It also uses MRI-guided coils to deliver the treatment, which is more precise than using anatomical markers to locate the target brain region, the left dorsolateral prefrontal cortex.

SAINT TMS devices will enter the market in 2023, but the excitement comes with a few limitations. We don't know how well the benefits will hold up, and the approach has not been independently validated or directly compared to traditional TMS.

Research Updates IN PSYCHIATRY

PTSD

Can CBD Work for PTSD?

Sin Yan Lo, PMHNP-BC. Ms. Lo, author of this educational activity, has no relevant financial relationship(s) with ineligible companies to disclose.

REVIEW OF: Bolsoni LI et al, *Psychopharmacology (Berl)* 2022;239(5):1499–1507

STUDY TYPE: Randomized double-blind, placebo-controlled trial

Marijuana contains close to 100 cannabinoids. Among them, tetrahydrocannabinol (THC) is responsible for marijuana's psychotogenic and rewarding effects, while cannabidiol (CBD) has some evidence to reduce psychosis and anxiety. Patients often take CBD as an oral supplement (CBD oil or gummies), and it is available as a prescription (Epidiolex) for rare forms of epilepsy. This study aimed to see if CBD can soothe symptoms of PTSD and disrupt memory consolidation of the trauma.

The double-blind trial randomized 33 subjects with PTSD to take either CBD or placebo while undergoing exposure exercises related to past trauma. Patients with a history of substance use or psychiatric disorders other than anxiety and depression were excluded. There were three total exposure sessions, each given one week apart.

During the exposure, the subjects listened to a 90-second recording of their traumatic experience and then imagined the trauma for 30 seconds (they recorded the 90-second narrative during the first session). The treatment was only given in the second exposure session, where subjects received either CBD 300 mg or placebo before undergoing the exposure. The intent was to test whether CBD could reduce PTSD symptoms after the exposure and whether the benefits, if any, persisted over the next week.

Symptoms were measured before and after the exposure. The primary outcome was change on a visual-analogue scale of anxiety, sedation, cognitive impairment, and discomfort. Secondary outcomes included the State-Trait Anxiety Inventory, a self-reported PTSD scale, and physiologic measures of blood pressure, heart rate, and salivary cortisol.

Those who took CBD reported improvement in cognitive symptoms (feeling capable, perceptive, better able to reason, physically agile, clear-headed, sociable, and resilient), and the effects were sustained for the week after taking it. However, it did not help with anxiety, alertness, or discomfort after recall of the trauma. There were no significant changes in blood pressure, heart rate, or salivary cortisol.

The main limitation here is the fact that the researchers used multiple tests without correcting for multiple comparisons. The sample size was also small, and comorbidities were not distributed evenly between the groups despite randomization.

CARLAT TAKE

The study provides some reassurance that CBD oil does not worsen and may improve PTSD, but the methodological flaws mean we're not ready to endorse its use.

TREATMENT RESISTANCE

Aripiprazole in Depression: The Right Dose

Richard Moldawsky, MD. Dr. Moldawsky has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

REVIEW OF: Furukawa Y et al, *Br J Psychiatry* 2022;221(2):440–447

STUDY TYPE: Meta-analysis of randomized controlled trials

Aripiprazole is FDA approved for antidepressant augmentation, and although it is the best-studied atypical antipsychotic for this condition, practitioners have not yet nailed down what dose to prescribe. Guidelines recommend anywhere from 2 to 15 mg/day, but higher doses bring additional risks like akathisia, sedation, and metabolic problems. This meta-analysis aimed to find the optimal dose range.

The authors found 10 double-blind, placebo-controlled, randomized studies in which aripiprazole was added to an SSRI or SNRI antidepressant in patients with treatment-resistant depression. The definition of treatment resistance varied among the studies, which required an inadequate response to 1–3 antidepressant trials and lasting at least 6–12 weeks. Patients with other psychiatric and substance use disorders were excluded, as were any who had received electroconvulsive therapy in the last 10 years or had been on adjunctive antipsychotics in the three weeks before starting aripiprazole.

This yielded 2,625 patients, 55% female. Over half the studies took place in North America and about a third were conducted in Japan. Some studies compared augmentation with aripiprazole using a fixed-dose schedule and others allowed flexible dosing. Trials lasted six to eight weeks. Doses ranged from 2 to 20 mg/day. Reduction in the Montgomery-Åsberg Depression Rating Scale was the main outcome measure. Tolerability (dropouts due to adverse effects) and acceptability (dropouts for any reason) were also tracked.

The main finding was that efficacy was associated with doses between 2 and 5 mg, with no additional benefits at higher doses. Aripiprazole 4 mg resulted in a 36% improvement compared with 23% on placebo. The odds ratio of response gradually increased as the dose increased from 2 mg (1.46) to 4 mg (1.87), then leveled off at 5 mg (1.91). Doses beyond 5 mg were well tolerated but didn't add clinical benefit.

One limitation is that the analysis involved multiple studies with varied doses that were not designed to test the hypothesis at hand. It is possible that some patients will do better at higher doses of adjunctive aripiprazole, but it is difficult to say who they are.

CARLAT TAKE

When using aripiprazole for antidepressant augmentation, 2–5 mg is the ideal range.

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CME Post-Test

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1. What nutrient has been shown to be beneficial when supplemented alongside the DASH diet? (LO #1)?
   [ ] a. EPA fatty acids [ ] b. DHA fatty acids [ ] c. Magnesium [ ] d. Iron
2. According to Dr. Pies, how much higher is the antidepressant switch rate into mania for patients with bipolar I disorder compared to bipolar II disorder (LO #2)?
   [ ] a. Twice as high
   [ ] b. Three times as high
   [ ] c. Four times as high
   [ ] d. The rates are equal
3. Which medications have positive evidence for treating symptoms of insomnia in ADHD (LO #3)?
   [ ] a. Zolpidem and melatonin
   [ ] b. Clonidine and eszopiclone
   [ ] c. Guanfacine and eszopiclone
   [ ] d. Melatonin and clonidine
4. What was the main limitation in a 2022 study that concluded cannabidiol may improve cognitive symptoms of PTSD, but does not help with anxiety after recollections of the trauma (LO #4)?
   [ ] a. The study lacked blinding in the subjects
   [ ] b. The study was not designed to test the hypothesis in question
   [ ] c. The study was not randomized
   [ ] d. Multiple tests were used without correcting for multiple comparisons
5. Artificial colorings, sodium benzoate, and chemicals like bisphenol A can negatively impact cognition in individuals with and without ADHD (LO #1).
   [ ] a. True [ ] b. False
6. According to Dr. DeBattista, what is the effect size of ketamine when used short term for treatment-resistant depression (LO #2)?
   [ ] a. No effect size
   [ ] b. Small effect size
   [ ] c. Medium effect size
   [ ] d. Large effect size
7. What effect does oxazepam have on opioids and stimulants (LO #3)?
   [ ] a. It enhances the opioid high and decreases the rewarding effects of stimulants
   [ ] b. It enhances the stimulant high and decreases the rewarding effects of opioids
   [ ] c. It enhances both the stimulant high and the rewarding effects of opioids
   [ ] d. It decreases both the stimulant high and the rewarding effects of opioids
8. What is the ideal daily dosage of aripiprazole when treating for antidepressant augmentation (LO #4)?
   [ ] a. 1–2 mg [ ] c. 6–10 mg
   [ ] b. 2–5 mg [ ] d. 9–15 mg

Research Updates

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PSYCHOPHARMACOLOGY

A Single Prescriber Reduces Risk of Overdose in Patients on Opioid and Benzodiazepine

Kamron Fariba, MD. Dr. Fariba, author of this educational activity, has no relevant financial relationship(s) with ineligible companies to disclose.

REVIEW OF: Chua KP et al, *JAMA Netw Open* 2021;4(8):e2120353

STUDY TYPE: Retrospective cohort study

When a patient on an opioid needs a benzodiazepine, should the two medications be handled by one prescriber or multiple prescribers? Among patients on opioids, one in five are also prescribed a benzodiazepine, but the combination raises the risk of opioid overdose fatalities four-fold. This study is the first to look at safety outcomes for single vs multiple prescribers.

Using a database of medical and pharmacy claims, researchers performed a retrospective cohort analysis, identifying patients who had one or more days of opioid-benzodiazepine overlap between January 1, 2017, and December 31, 2018.

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Ultimately, the cohort included 529,053 patients, ages 12 years and older, with an average age of 61. Researchers determined whether the opioids and benzodiazepines were prescribed by a single clinician or by two or more clinicians. The primary outcome measure was the occurrence of an overdose.

The relative overdose risk, adjusted for prescribing patterns, demographics, and comorbidities, was 1.2 times greater when the opioid-benzodiazepine overlap involved multiple prescribers vs a single prescriber (unadjusted overdose risk was 1.8 times greater), which translates to a 20% increased risk of overdose.

The main limitation is the study's design, which cannot prove causation. Also, the cohort was restricted to insured patients, and overdose deaths may have been underreported.

CARLAT TAKE

Opioid and benzodiazepine combinations are risky, but the risk goes down when one clinician monitors both scripts. It's easier to detect problematic use with that arrangement, particularly when the prescriber is a pain specialist, as they require a higher level of scrutiny, including urine drug screens and pill counts. If you're concerned about the overdose risk in a patient taking both an opioid and a benzo, arranging for them to get both prescriptions from the same physician is a reasonable option.

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