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Chris Aiken, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Living With Mental Illness

Learning Objectives

After reading these articles, you should be able to:

1. Identify the risks and benefits of omega-3 fatty acids for psychiatric disorders.
2. Differentiate between the biopsychosocial and perspectives models of psychiatry.
3. Discern how and whether a cognitive behavioral therapy app will benefit patients with insomnia.
4. Summarize some of the current research findings on psychiatric treatment.

How to Prescribe Omega-3 Fatty Acids

Chris Aiken, MD. Editor-in-Chief of TCPR. *Practicing psychiatrist, Winston-Salem, NC.*

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

Highlights From This Issue

- New research suggests most omega-3s have the wrong formulation, and we show you how and when to use them.
- Dr. Margaret Chisolm describes an assessment tool developed at Johns Hopkins that blends the DSM with other perspectives in psychiatry.
- The FDA has cleared the first prescription insomnia app, and we detail how (and whether) to use it.

Omega-3 fatty acids ("fish oil") claim broad benefits in physical and mental health and have even made it into a few treatment guidelines in psychiatry. But most products on the shelf do not have the right ingredients for psychiatric use. In this article, I'll review how and when to use omega-3s.

Mechanism

Omega-3s are "essential fatty acids," meaning we cannot produce them on our own and must obtain them from our diet. In the brain, they coat nerve cell membranes and have neuroprotective and anti-inflammatory effects. Most modern diets are deficient in omega-3s, and serum omega-3 levels are particularly low in people with psychiatric disorders. However, it's not clear that omega-3s work better in people with deficiencies, so testing serum levels is not yet recommended.

Omega-3 augmentation of antidepressants

Omega-3s have the most robust research in depression, with over 40 randomized controlled trials (RCTs) involving around 10,000 participants. Some of those

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Q&A With the Expert

Mental Illness and Flourishing
Margaret Chisolm, MD

Vice Chair for Education in Psychiatry and Behavioral Sciences at Johns Hopkins University. Author of From Survive to Thrive: Living Your Best Life With Mental Illness *(2021).*

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

Photo credit: Greg Dobler

TCPR: You and other psychiatrists at Johns Hopkins have a way of viewing mental illness that differs from the biopsychosocial model. Tell us about that.

Dr. Chisolm: We use a model called "perspectives of psychiatry" that was developed by Paul McHugh and Phillip Slavney in the 1970s. It's really a framework that considers the origin of patients' problems through four lenses:

1. Disease perspective: Clinical syndromes that emerge from a "broken brain" (structure or function that has gone awry), like schizophrenia or bipolar disorder.

2. Dimensional perspective: Personality, temperamental, or cognitive traits that are universal, graded, and measurable, like neuroticism or intellectual disability.

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Expert Interview

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3. Behavior perspective: Behaviors that are reinforced by conditioned learning that increases drive and narrows choice, like anorexia nervosa or addiction.

4. Life story perspective: How people construct meaning or deal with recent or past events, like the loss of a loved one or sexual trauma.

TCPR: Are some conditions better suited to particular lenses?

Dr. Chisolm: It might seem natural to view traumatic brain injury through the disease perspective; addictions and eating disorders through the behavior lens; personality as a dimension; and adjustment disorder as part of the life story. But the idea is that we gain a broader understanding of the origins of a patient's problems, and can see new solutions, when we consider the patient's presentation from all four perspectives.

Five-Factor Model of Personality	
Neuroticism	Sensitive, nervous, and emotionally reactive vs resilient and confident
Extroversion	Outgoing and energetic vs solitary and reserved
Agreeableness	Friendly, flexible, and compassionate vs critical and rational
Openness to experience	Inventive, creative, and curious vs consistent and cautious
Conscientiousness	Efficient and organized vs extravagant and careless

TCPR: Can you give an example of how we might examine a specific problem from multiple perspectives under this model?

Dr. Chisolm: If someone with bipolar disorder has depression, we'd understand that mood episode has its origins in a broken structure or function in the brain (disease), but the episode could also have been partially precipitated by the interaction between perhaps a neurotic temperament and a particularly stressful provocation (dimensional), and/or, say, the person's problematic drinking (behavior), and/or the person's demoralization from having received the diagnosis of bipolar disorder (life story). Usually, at least two, if not three, of these perspectives are relevant to explaining the origin of a patient's problems, and sometimes all four are at play.

TCPR: Do you use all four perspectives with every patient?

Dr. Chisolm: Absolutely. Sometimes I engage the patient in the process. I say, "This is how I think about things. Is it something you have? Is it because of who you are? Is this because of something you're doing? Is this because of something you've encountered? How do you explain what's going on?" Often they'll say, "It's all of the above." And then I share my perspective with them, which might include diagnosis of a disease, assessment of the role of affective temperaments, identification of maladaptive conditioned behaviors, and discussion of the role of certain events in their life story.

TCPR: What are some questions that help you assess the dimensional perspective?

Dr. Chisolm: That one is the most challenging. I use the five-factor or "big five" model of personality, but I don't give the official test (it is available at www.personal.psu.edu/~j5j/IPIP) *(Editor's note: See the "Five-Factor Model of Personality" table above).* Instead, I use questions. For neuroticism, which is about strongly felt emotions, I might ask, "Are you a sensitive person who feels things really strongly?" For introversion/extroversion, I might ask, "If you are at a party and say the wrong thing, is that something that you dwell on a lot, or is it like water off a duck's back?"

TCPR: What about the three other dimensions?

Dr. Chisolm: The openness dimension is a little more challenging. People with high levels of openness might have interests in art or abstract activities; they may be cultural explorers or physical risk-takers. For agreeableness, I ask about flexibility, such as, "Do you have problems adjusting when somebody changes plans at the last minute?" For conscientiousness, I ask, "How do you feel when somebody breaks a promise?" or, for the opposite of this trait, "Is your partner always nagging at you to pick up your socks or be cleaner and more orderly?" It's also useful to get this information from family members because if the patient is in a depressed state, their answers may not be able to tell you much about their real personality due to the cognitive distortions that sometimes come with depression.

TCPR: How do you ask about the life story perspective?

Dr. Chisolm: The life story perspective is all about the meaning people give to events. For example, if their infant died of SIDS, I may ask, "How are you dealing with the loss? How do you understand it? How do you explain it?" They may blame themselves, or they may have a religious understanding of it. Part of the work is helping them rescript their story collaboratively. I might say, "You know, maybe there are other ways of looking at this. Could this be a random act of tragedy? How are you going to make meaning of this in terms of why it happened?"

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Expert Interview
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TCPR: Do you assign tasks to help a patient rescript their story?

Dr. Chisolm: Journaling might be helpful, but I don't typically assign homework because a lot of the people I see simply don't do it. We do a lot of the work in session. I offer up interpretations, but I try to be very tentative about that and remain neutral and collaborative. This is the patient's story. We have a lot of power as psychotherapists/psychiatrists, and I really don't like to impose a story on someone. Many patients will simply agree with a story you tell, and that usually isn't very helpful.

TCPR: What questions help you get at the behavior perspective?

Dr. Chisolm: I divide behaviors into innate and acquired drives. Innate drives include things we all do, like sleep, sex, and eating, and I screen for problems in each of those areas. Acquired drives include self-harm, which often has a behavioral conditioning component; substance use disorders; and digital addictions. If they have problems with any of these behaviors, I get all the details. I ask, "When do you drink? What role does drinking play in your life?" Or I ask, "What do you fantasize about sexually? Do you use pornography?"

TCPR: It sounds like these perspectives might help patients see other solutions for their problems—such as behavioral treatments for insomnia instead of just using hypnotics.

Dr. Chisolm: Definitely. This work helps patients think about their problems more broadly. It also helps with stigma because it gives alternatives to the disease model, which many patients find stigmatizing. It's often much more affirming to talk about personality from a dimensional perspective with strengths and weaknesses than to label it a personality disorder. So, for neuroticism I may say, "You have an extra dose of feeling compared to the average person, and that works great in some situations but not so well in others."

"It's often much more affirming to talk about personality from a dimensional perspective with strengths and weaknesses than to label it a personality disorder. So, for neuroticism I may say, 'You have an extra dose of feeling compared to the average person, and that works great in some situations but not so well in others.'"

Margaret Chisolm, MD

TCPR: What are some strengths of neuroticism?

Dr. Chisolm: If they notice a bump on their skin, they're likely to go straight to a doctor about it, so they may catch problems earlier than someone who doesn't worry much.

TCPR: This model sounds like it's a way of looking at problems. What about a model of health?

Dr. Chisolm: For that, I'm more influenced by Tyler VanderWeele's model of flourishing. Well-being—or flourishing—is more than the absence of mental illness. In fact, people can flourish in the face of mental illness. Flourishing encompasses feelings of happiness and life satisfaction, physical health, meaning and purpose, character and virtue, and close social relationships. These domains of flourishing are pretty similar to what philosophers have talked about for millennia when considering the question of what it means to lead a good life. Dr. VanderWeele wanted to know how someone could achieve this state of flourishing. He wanted to understand the pathways to the good life (VanderWeele TJ, *Proc Natl Acad Sci U S A* 2017;114(31):8148–8156; VanderWeele TJ et al, *JAMA* 2019;321(17):1667–1668).

TCPR: What did he arrive at?

Dr. Chisolm: He used an empirical approach—drawing causal links from large epidemiologic data sets—and identified four pathways to flourishing: family, community, work, and education. For community, he focused on religious community because that is where we have a lot of epidemiologic data. So, helping people strengthen where they are on these four flourishing pathways will support them in their quest not only for mental health, but also for overall well-being. Everyone wants to lead a good life, and a mental illness shouldn't be an obstacle to leading the best life possible.

TCPR: Is flourishing something you address after recovery?

Dr. Chisolm: Not necessarily. Some patients don't reach full recovery despite our best efforts, but they can still flourish through supportive family, being part of the community, getting meaningful work, and pursuing education at the level they are capable of. In schizophrenia, people's abilities are usually not what they were before their illness began. Maybe their cognition is impaired, but they can still form close relationships, take care of their physical health, and find some meaning and purpose in a job or other activities. I also think patients are more likely to adhere to their medications or stay sober if these pathways are in place—if they have a reason to live and someone who cares how they are doing.

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

How to Prescribe Omega-3 Fatty Acids
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studies were negative, but the results demonstrate a pattern that can inform practice. First, their antidepressant effects were only clear when the trials involved clinically diagnosed, DSM-based depression instead of nonspecific depressive symptoms. Second, only the trials that used a specific ratio of omega-3s were positive in meta-analyses (Hallahan B et al, *Br J Psychiatry* 2016;209(3):192–201).

There are two types of omega-3s: EPA and DHA (eicosapentaenoic acid and docosahexaenoic acid). The formulations that work either are pure EPA or contain at least twice as much EPA as DHA (Guu TW et al, *Psychother Psychosom* 2019;88(5):263–273). These formulations

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have been shown to be effective when augmenting standard antidepressants, but their efficacy is mixed when given alone. As augmenting agents, their effect size is medium (0.5–0.6), similar to the effect of the average psychiatric treatment.

We don't know much about who will respond to omega-3s, but one controlled trial points to patients with inflammation (ie, those with a high-sensitivity C-reactive protein level > 3 mg/L). In that study, only the depressed patients with elevated inflammatory biomarkers responded to omega-3s, and the higher the inflammation, the better the response (for more on assessing inflammation, see *TCPR* Jan 2019) (Rapaport MH et al, *Mol Psychiatry* 2016;21(1):71–79).

Omega-3s are also effective as augmentation of mood stabilizers in bipolar depression, but here the research is not as robust, with seven RCTs. In mania, their benefits were small and nonsignificant (Grosso G et al, *PLoS One* 2014;9(5):e96905).

Other uses

After depression, the best evidence for omega-3s is in ADHD, borderline personality disorder, and schizophrenia. In children and adolescents with ADHD, omega-3s improved both the core symptoms of the disorder and associated features like emotional lability and conduct problems (seven RCTs, total n = 534; Chang JP et al, *Neuropsychopharmacology* 2018;43(3):534–545). In borderline personality disorder, they lowered affective dysregulation and impulsivity (four RCTs, total n = 137, Karaszewska DM et al, *J Clin Psychiatry* 2021;82(3):20r13613). In schizophrenia, omega-3s worked best in the early phase of the illness, where they improved negative symptoms and reduced white matter abnormalities (nine RCTs, total n = 571; Chen AT et al, *Ann Clin Psychiatry* 2015;27(4):289–296).

The finding that omega-3s work better in the early phase of schizophrenia raises the possibility that they may prevent mental illness. That was born out in a remarkable study from Vienna of 81 adolescents with mild psychotic symptoms and genetic risk factors for schizophrenia. The teens were treated with either a three-month course of omega-3s or placebo. A year after this brief inoculation, only 5% of the omega-3 group converted to schizophrenia, compared to 28% of controls. Seven years later, the rates were 10% vs 40% (with 80% retention of patients; Amminger GP et al, *Nat Commun* 2015;6:7934). Two other trials attempted to confirm this finding—one positive and one negative—but the negative study only followed patients for six months. The preventative potential of omega-3s has not been tested in bipolar disorder, but omega-3s did have therapeutic effects in high-risk teens with mild manic symptoms and strong family histories of bipolar disorder (Fristad MA et al, *J Child Adolesc Psychopharmacol* 2015;25(10):764–774).

Other controlled trials suggest that omega-3s reduce nonspecific irritability in healthy populations, including prisoners, married couples, elderly Thai men, and college students taking final exams (Sinn N et al, *Nutrients* 2010;2(2):128–170).

Omega-3 Fatty Acids (Fish Oil)	
Main use	Augmentation in unipolar and bipolar depression.
Other uses	ADHD, borderline personality disorder, negative symptoms of schizophrenia in the early phase of the disorder, and nonspecific irritability.
Dosage	Use a product with either 100% EPA or ≥ 2:1 ratio of EPA:DHA. Start 1,000 mg/day (total of EPA+DHA). If no response after a month, titrate to a maximum of 3000 mg/day.
Side effects	Nausea, belching, fishy taste.

Recommended Omega-3 Products		
Product	**EPA/DHA in One Capsule**	**Monthly Cost for ~1000 mg/day**
High concentration (starting dose one capsule/day)		
Carlson Elite EPA Gems	1000/16.5 mg	$15
GNC Triple Strength	734/266 mg	$8
Nature Made 1400	683/252 mg	$9
Nordic Naturals ProOmega (Liquid)	1950/975 mg	$22
NutriGold Triple Strength	725/275 mg	$11
OmegaVia Ultra Concentrated	780/260 mg	$15
Spring Valley Maximum Care 2000 (Walmart)	645/310 mg	$4
Vascepa (Rx only)	960/40 mg	$30
Low concentration (starting dose two capsules/day)		
OmegaVia EPA 500	500/21.2 mg	$15
Vitacost Super EPA (vitacost.com)	600/150 mg	$16

Source: ConsumerLabs

Physical risks and benefits

Omega-3s are well tolerated with side effects of nausea, belching, and fishy taste (see table at left). These improve by choosing an enteric-coated or odor-neutralized product and refrigerating the capsules. Omega-3s may prolong bleeding time, a problem for patients undergoing surgery or taking anticoagulants, but this risk was not detectable at the doses used in psychiatry (< 4000 mg/day; Mori TA, *Food Funct* 2014;5(9):2004–2019). The FDA warns of possible arrhythmias with high-dose omega-3s in patients with atrial fibrillation.

One study found a correlation between omega-3 serum levels and prostate cancer, but other research refutes this or even shows the opposite effect, and the association might be explained by contaminants in dietary fish (Aucoin M et al, *Integr Cancer Ther* 2017;16(1):32–62). Contamination by heavy metals like mercury is a concern with fish oil, and the products we've recommended in the table at the top of the page were tested for metal contamination.

Omega-3s also have health benefits, and several prescription products are FDA indicated for lowering triglycerides. They also have evidence in hypertension, inflammatory bowel disease, dry eyes, macular degeneration, fatty liver, arthritis, asthma, and psoriasis (including psoriasis due to lithium). The doses in medical disorders are often on the high side (3000–4000 mg/day of EPA+DHA for psoriasis and elevated triglycerides).

Diet or supplement?

Technically, patients could get a clinical

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A Prescription App for Insomnia

Jesse Koskey, MD. Psychiatrist at Sensible Care, CA.

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

You may recommend smartphone apps for mindfulness, symptom tracking, or medication reminders, but do you *prescribe* apps? FDA-authorized "prescription digital therapeutics" are already available for ADHD (EndeavorRx), traumatic nightmares (Nightware), and opioid use disorder (reSET-O). Now Somryst, a prescription app for insomnia, joins them. It is designed to provide adults with a personalized, six- to nine-week course of cognitive behavioral therapy for insomnia (CBT-I). Should we recommend more phone time for patients who already can't sleep well? And if so, how are apps prescribed?

CBT-I: What the evidence shows

CBT-I includes standard sleep hygiene measures but takes that basic therapy one step further by adding in "bed restriction." In this step, patients calculate the average time they spend asleep in bed over a week and then limit their time in bed to that average (plus a 30-minute buffer to fall asleep). At first, bed restriction leaves patients drowsy, but as that drowsiness builds up over time it helps them fall asleep faster, and as their sleep improves, they are allotted more time in bed.

Over 20 randomized controlled trials (RCTs) have evaluated CBT-I. Together, they find that CBT-I helps patients fall asleep 19 minutes earlier and wake up 26 minutes less overnight, in addition to improving sleep efficiency (time spent in bed asleep vs awake) by about 10% compared to controls (Trauer JM et al, *Ann Intern Med* 2015;163(3):191–204). Other trials show that CBT-I is more effective than sleep hygiene, and even has an edge over sleep medications. Several medical groups, including the American Academy of Sleep Medicine and the American College of Physicians, recommend it first line for insomnia.

Therapists who practice CBT-I are hard to find, which is where digital adaptations of CBT-I come in. Digital CBT-I generally works as well as the face-to-face format, though patients who struggle with motivation may do better with a personal therapist. A 2017 Dutch RCT comparing a proprietary CBT-I app to a waitlist control found that insomnia severity, waking after falling asleep, total sleep time, and sleep efficiency improved over the course of six weeks for the app users compared to controls (Horsch CH et al, *J Med Internet Res* 2017;19(4):e70).

Is there any evidence for the new Somryst app? Not directly, but an earlier web-based version of Somryst, called SHUTi, was tested in several controlled trials. For example, a 2016 randomized trial that compared SHUTi to an online educational control found both immediate and one-year improvements with SHUTi in sleep efficiency, overnight wakefulness, and sleep quality, although total sleep time was not statistically different from controls (Ritterband LM et al, *JAMA Psychiatry* 2017;74(1):68–75). The SHUTi data were impressive enough to eventually earn FDA authorization for Somryst.

How Somryst works

Somryst consists of a nightly sleep diary and six weekly "cores." These are sequential CBT-I lessons that present, review, and summarize concepts, as well as assign and review homework. Graphs, animations, vignettes, and quizzes keep patients engaged. As long as patients complete the prior week's material, they unlock new cores each week, starting with an overview and working through sleep behavior, sleep education, sleep thoughts, and problem prevention. As patients provide Somryst with their sleep diaries and complete the cores, the program algorithmically generates nightly sleep schedules, without input from a therapist. The app also graphs sleep data and rating scales (Thorndike FP et al, *E J Appl Psychol* 2008;4(2):32–42).

The main competitor to Somryst is CBT-i Coach, a free app developed for the Veterans Administration (www.tinyurl.com/2p8v3x9y). Unlike Somryst, CBT-i Coach was intended to be used with guidance from a therapist, but motivated patients can also use it on their own. CBTi Coach improved insomnia and sleep quality in two prospective but uncontrolled studies (Reilly ED et al, *JMIR Form Res* 2021;5(12):e29573).

Risks

Because CBT-I restricts time in bed, Somryst lists contraindications for conditions that might worsen with sleep deprivation: epilepsy, bipolar disorder, parasomnias, untreated obstructive sleep apnea, and jobs involving heavy machinery, among others. However, CBT-I has been used successfully in treated sleep apnea, and a controlled trial showed that a modified form of CBT-I improved insomnia in euthymic bipolar disorder. CBT-I also improved mood and augmented antidepressants in controlled trials of unipolar depression.

Somryst is only available to patients 22 or older, likely in recognition that youths are particularly vulnerable to the risks of phone addiction. In a recent survey of 1,000 university students, one in three reported that excessive smartphone use impaired their sleep (Sohn SY et al, *Front Psychiatry* 2021;12).

How to use Somryst

Providers can prescribe Somryst after setting up an online account in Pear Therapeutic's Pear Connect system at www.somrysthcp.com or 833-697-3738, or through digital pharmacies like Truepill, if their EHR interfaces with it. Alternatively, patients can obtain a prescription directly through www.somryst.com, which connects them to a Pear Therapeutics–contracted telemedicine provider who ensures the patient has a diagnosis of insomnia and no contraindications.

Patients then download Somryst from their app store and use the prescription code to unlock the app. From that point, they have nine weeks to use Somryst before the code deactivates.

Some insurers cover Somryst, including Optum and Serve You Rx, but only for a diagnosis of chronic insomnia. Patients whose insurance does not cover Somryst may be eligible for a "Somryst Savings Card" from Pear, which brings the cost to $100 from the out-of-pocket cost of $900.

TCPR VERDICT: For a long time, the first-line treatment for insomnia (CBT-I) has not been available for most patients. Digital apps like Somryst and CBT-i Coach bring this therapy closer to home.

Research Updates IN PSYCHIATRY

SCHIZOPHRENIA

Vitamin B6 Lowers Prolactin on Antipsychotics

Brian Miller, MD, PhD, MPH. Dr. Miller has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

REVIEW OF: Zhuo C et al, *Front Psychiatry* 2021;12:681418

STUDY TYPE: Randomized, double-blind trial with an active control

Hyperprolactinemia, a common problem on antipsychotics, can cause multiple issues, including sexual dysfunction and gynecomastia. It is a particular problem in treatment-resistant schizophrenia (TRS), as these patients often need higher antipsychotic doses that are more likely to elevate prolactin. Dopamine agonists like bromocriptine can reverse the effect, as can low doses of the dopamine partial agonist aripiprazole (that's right, this antipsychotic actually treats hyperprolactinemia)—but beyond that, there is limited evidence for other treatment options. Vitamin B6 showed potential in earlier research, and this study tested that treatment in a large controlled trial.

This trial, run in China, tested high-dose vitamin B6 against an active control (low-dose aripiprazole) in 200 men ages 20–40 with TRS and hyperprolactinemia. Patients received either aripiprazole 5 mg twice daily or vitamin B6 300 mg twice daily, in addition to their current antipsychotic, for 16 weeks. Hyperprolactinemia was defined as a prolactin level > 25 µg/L, the usual cutoff for this diagnosis. Prolactin levels, psychotic symptoms, and cognition were assessed at baseline and every four weeks after study initiation. A total of 97% of subjects finished the trial.

Patients randomized to vitamin B6 were much younger, had higher levels of education, and had significantly higher prolactin levels at baseline (95.5 vs 89.1 µg/L) than the aripiprazole group. After 16 weeks, the vitamin B6 group showed a greater reduction in prolactin levels compared to the aripiprazole group (68.1% vs 37.4%). Both groups showed steep reductions in prolactin levels from baseline to week four, but the efficacy of aripiprazole plateaued after week eight, whereas vitamin B6 further reduced prolactin levels through week 16. Also, after 16 weeks, the vitamin B6 group showed a greater reduction in psychotic symptoms (17.8% vs 12.0%) and improvement in cognition (10% vs -5.4%) compared with the aripiprazole group, respectively. Vitamin B6 was well tolerated, with fewer side effects than in the aripiprazole group. Vitamin B6 also had favorable metabolic effects, as it did not increase blood glucose or lipids.

Limitations of the study include the fact that all subjects were male and had TRS. Therefore, the generalizability of findings to other patients and phases of illness is limited.

TCPR'S TAKE

Vitamin B6 may be a viable treatment option for antipsychotic-induced hyperprolactinemia, at least in TRS.

DEPRESSION

Oral Zuranolone for Postpartum Depression

Michael Posternak, MD. Dr. Posternak has disclosed no relevant relationships or financial interests in any commercial company related to this educational activity.

REVIEW OF: Deligiannidis KM et al, *JAMA Psychiatry* 2021;78(9):951–959

STUDY TYPE: Randomized controlled trial

DSM-5 defines postpartum depression (PPD) as any major depressive episode that begins during pregnancy or within four weeks after giving birth. Traditional antidepressants have long been used during this period, but only small studies supporting their efficacy exist and none have received FDA approval for this use. Brexanolone (Zulresso) is a neuroactive steroid that was approved by the FDA for PPD in 2019. However, this steroid requires 60 hours of continuous intravenous infusion as well as around-the-clock monitoring due to concerns for potential serious adverse effects such as loss of consciousness.

Zuranolone is an investigational medicine that is structurally similar to brexanolone but can be given orally. Both drugs work on the gabanergic system in a way that is distinct from benzodiazepines, and both are structural analogs of allopregnanolone (just as levothyroxine is a synthetic analog of the naturally occurring hormone thyroxine). This was a Phase 3 study testing the safety and efficacy of zuranolone for PPD.

In this trial, 151 women who developed new-onset depression either during their third trimester of pregnancy or within four weeks after giving birth were enrolled. Patients were randomized to receive either zuranolone 30 mg or placebo over the course of two weeks. The primary outcome measure was improvement on the Hamilton Depression Rating Scale, and assessments were made on days three, six, nine, 15, and 45.

On day 15, which was the primary date of interest, depression scores were significantly lower in the zuranolone cohort compared to placebo (-17.8 points vs -13.6 points; p = 0.003; effect size 0.53). Statistically significant effects were apparent as early as day three and were maintained through day 45, which was a full four weeks after treatment had been completed. Significant improvements were also seen in anxiety and global functioning, as well as maternal functioning. Zuranolone was well tolerated with the most common side effects being somnolence (15%), headaches (9%), and dizziness (8%), although none of these rates differed much from placebo.

The major limitation of this study is that breastfeeding women were not included, so zuranolone cannot yet be recommended for these patients. Furthermore, it remains to be seen whether the benefits of zuranolone are sustained beyond four weeks post-treatment.

TCPR'S TAKE

Zuranolone appears to be a safe and effective option for PPD. Encouragingly, its benefits appear to occur rapidly, and a two-week course of treatment may be all that is needed. The manufacturer plans to file for FDA approval in 2022. If it comes to market, it will offer a much more pragmatic option than brexanolone.

CME Post-Test

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1. In recent studies, omega-3 augmentation of antidepressants improved DSM-based depression with which effect size (LO #1)?
   - [ ] a. A small effect size
   - [ ] b. A medium effect size
   - [ ] c. A large effect size
   - [ ] d. Add-on omega-3s did not significantly improve depression

2. According to Dr. Chisolm, which element of the "perspectives of psychiatry" model is used when assessing the contributions of personality traits to the origin of a patient's problem (LO #2)?
   - [ ] a. Behavior perspective
   - [ ] b. Life story perspective
   - [ ] c. Dimensional perspective
   - [ ] d. Disease perspective

3. A 2021 survey of university students revealed that one in three students have impaired sleep related to their excessive smartphone use (LO #3).
   - [ ] a. True
   - [ ] b. False

4. In a recent study of antipsychotic-induced hyperprolactinemia in men with treatment-resistant schizophrenia, which of the following was concluded about the efficacy of vitamin B6 versus aripiprazole (LO #4)?
   - [ ] a. The aripiprazole group had a much greater reduction in prolactin levels at week 16
   - [ ] b. The vitamin B6 group had a significantly greater reduction in prolactin levels at week 16
   - [ ] c. Reductions in prolactin levels plateaued after week eight in the vitamin B6 group, but aripiprazole further reduced prolactin levels through week 16
   - [ ] d. Both treatment groups had similar reduction in prolactin level

5. According to recent studies, which of the following statements about omega-3s for psychiatric disorders is true (LO #1)?
   - [ ] a. Omega-3s have no benefits in the early phase of schizophrenia
   - [ ] b. Omega-3s have large and significant benefits in mania
   - [ ] c. Omega-3s produce the greatest response in depressed patients with low levels of inflammatory biomarkers
   - [ ] d. Only the trials of depression that used omega-3 formulations containing either 100% EPA or ≥ 2:1 ratio of EPA:DHA were positive in meta-analyses

In Brief: A Longer-Acting Lorazepam

Lorazepam (Ativan) received a new coating this year as Loreev XR, which promises a 24-hour duration for this benzodiazepine that is otherwise divided in two or three daily doses. It joins alprazolam (Xanax) as the only benzos with extended-release (XR) formulations (clorazepate ventured into this territory as Tranxene SD in 2002, but that medication is no longer manufactured).

For patients who require 24-hour coverage, these formulations offer convenience and—in theory—better tolerability and lower abuse liability. How well does that theory pan out? For lorazepam XR, we can only guess, as the approval was based on pharmacokinetic data in healthy volunteers and the drug lacks clinical studies. For alprazolam XR, a small trial does bear it out.

Fourteen men with a history of sedative abuse were given blinded samples of alprazolam XR, alprazolam instant release (IR), and placebo. When asked how much they were willing to pay for another dose, XR and placebo earned the same valuation, but IR attracted a higher price (no money was exchanged in the study). Side effects also looked better with XR, which—unlike IR—did not impair cognitive or motor function (Mumford GK et al, *Clin Pharmacol Ther* 1995;57(3):356–365).

Lorazepam XR's pharmacokinetics suggest it may have similar advantages. Alprazolam and lorazepam peak in 1.5–2 hours in their IR forms, while the XRs have a longer delay: nine hours for alprazolam XR and 14 hours for lorazepam XR. The two XRs differ, however, in how they interact with food. Lorazepam XR lacks food interactions, but a high-fat meal will cause alprazolam XR to release its contents faster, resulting in a faster speed of onset and—potentially—withdrawal effects before the next dose is due.

Alprazolam XR has the advantage of FDA approval in panic disorder (typical dose 2–5 mg/day, maximum 10 mg/day), an approval shared only by clonazepam (typical dose 1–2 mg/day, maximum 4 mg/day). Panic disorder is the best-studied indication for benzodiazepines and one where 24/7 coverage is sometimes needed for patients to function.

Lorazepam, however, has advantages of its own. It lacks hepatic drug interactions and does not form active metabolites, making it potentially safer in the elderly and medically ill. It also has one of the lowest toxicity indexes among the benzos, a quality that's particularly relevant given the new warnings about accidental overdoses when benzodiazepines are taken with opioids. Alprazolam's toxicity index is one of the highest (Buckley NA and McManus PR, *Drug Saf* 2004;27(2):135–141). However, the risk of dangerous opioid interactions is higher with long half-lives and XR formulations, so the IR formulation is preferable for the rare cases where a benzo and an opioid must be taken together.

Lorazepam XR is available as 1, 2, and 3 mg capsules that can be opened and sprinkled on food. It is dosed once in the morning at a monthly cost of $300.

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

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How to Prescribe Omega-3 Fatty Acids

Continued from page 4

dose of omega-3 in their diet by eating a six-ounce serving of oily fish like salmon, herring, or anchovies twice a week. Other dietary sources include walnuts, flaxseeds, edamame, fruits, and dark green vegetables. Dietary sources do not have enough EPA to match the clinical dose, but that does not mean they won't help. These foods contain other nutrients that improve brain health, and they were highly represented in the recent studies of diet in depression (see *TCPR* November/December 2021: "Nutritional Psychiatry in Practice" with Drew Ramsey, MD).

The "Recommended Omega-3 Products" table on page 4 lists products with the proper EPA:DHA ratio from manufacturers whose quality was approved by ConsumerLabs. Only one prescription product (Vascepa) contains enough EPA, and no vegetarian options have enough EPA for psychiatric use. Some products also contain omega-7s, which appear benign. Omega-7s are found in the diet and do not have significant risks or benefits.

TCPR VERDICT: Consider omega-3s as an adjunct to medication for depression, bipolar depression, ADHD, borderline personality disorder, and negative symptoms of schizophrenia, but make sure to choose a reliable product with a high amount of EPA.

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