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Chris Aiken, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month: **ADHD**

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

1. Identify the challenges in diagnosing later-onset ADHD.
2. Evaluate the effectiveness of using micronutrients to improve patients' mental health.
3. Instruct patients on the effective use of lightbox therapy for treating photosensitive disorders such as depression.
4. Summarize some of the current research on psychiatric treatment.

Adult-Onset ADHD

Michael Posternak, MD. Psychiatrist in private practice, Boston, MA. Chris Aiken, MD. Editor-in-Chief of The Carlat Psychiatry Report. *Practicing psychiatrist, Winston-Salem, NC.*

Dr. Posternak and Dr. Aiken have disclosed that they have no relevant financial or other interests in any commercial companies pertaining to this educational activity.

"My son was just diagnosed with ADHD, and I think I may have it, too," says Alex, a 42-year-old salesman who presents for evaluation. In addition to being sad, anxious, and irritable, and meeting criteria for mild major depression, Alex says he is often bored at work, fidgety during meetings, and forgetful at home. He has had these problems since early college, and they fulfill the criteria for ADHD except that they are not traceable to his childhood.

Alex's presentation will sound familiar to anyone who has treated ADHD. DSM-5 requires that ADHD symptoms begin before age 12, but there's a new concept out there called "adult-onset ADHD." So what do we make of his presentation? Is this really ADHD, or are the cognitive complaints a result of other causes such as stress, depression, and

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Highlights From This Issue

Micronutrients are vitamins and minerals that play an essential role in human physiology. They have promising studies in a host of psychiatric disorders, and Dr. Rucklidge explains why.

Adult-onset ADHD has been proposed as a new diagnosis, but the data supporting it point in a different direction.

Light therapy is one of few natural treatments with an efficacy that compares well to medication. Inside is a guide to using it in depression and bipolar disorder.

New medications for schizophrenia (Secuado) and narcolepsy (Wakix) are reviewed.

Q&A With the Expert

Micronutrients in Mental Health
Julia Rucklidge, PhD

Professor, University of Canterbury, New Zealand

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

TCPR: You've studied micronutrients in ADHD and other psychiatric disorders. What are micronutrients?

Dr. Rucklidge: They are small nutrients—vitamins, minerals, and amino acids—that are essential for your brain to function optimally. They include cofactors like B6, zinc, and magnesium that are involved in the synthesis of neurotransmitters and hormones. Patients take them in pills that contain a broad spectrum of these nutrients. Some are available by prescription, like EnLyte, and others are over the counter, like EMPowerplus or Daily Essential Nutrients. So you might see patients who are taking them already.

TCPR: How are these different from multivitamins?

Dr. Rucklidge: When people think of multivitamins, they think of over-the-counter pills for general health and well-being. What we have studied is quite different. Micronutrients are much more substantial in

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Adult-Onset ADHD

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anxiety? To better understand this question, let's start with some history.

History of the ADHD diagnosis

Early descriptions of ADHD date back to 1902, but the diagnosis really got its start in 1937 when Charles Bradley published the first report of amphetamine on behavioral problems and school performance. Over the years, the names of this syndrome have changed: minimal brain dysfunction (1960s–1970s), ADD (1980–1994), and ADHD (1994–present). Throughout these changes, ADHD has always been depicted as a neurodevelopmental disorder, which means that—in the words of DSM-5—"ADHD begins in childhood." Earlier DSM versions required that the symptoms begin before age 7, but DSM-5 relaxed the criteria to age 12.

Part of the reason for this change was that it's difficult for older patients to recall their kindergarten years. There is also little difference between children who develop ADHD before age 7 and those who develop it between ages 8 and 12. They look similar in terms of family history, neuropsychological testing, psychiatric comorbidity, functional impairment, and course of illness (Faraone SV et al, *Am J Psychiatry* 2006;163(10):1720–1729; Willoughby MT et al, *J Am Acad Child Adolesc Psychiatry* 2000;39(12):1512–1519). That has caused some to speculate that ADHD symptoms beginning in the teen years, or even the adult years, may also represent the same syndrome.

Teen-onset ADHD

ADHD symptoms are difficult for patients to recall, so the best way to capture their true onset is to follow people prospectively over time. Three recent studies have done that. They followed a large cohort from early childhood to age 18 with regular assessment of ADHD and other symptoms, including parent and teacher reports. All of these found new-onset ADHD in the late teenage years after ruling out other causes of ADHD symptoms.

Is it possible that the studies missed the early presentation? Maybe. In one study, most of the teen-onset cases (75%) had sub-threshold ADHD symptoms before age 12, suggesting that they might represent a delayed onset of the full disorder (Cooper M et al, *J Child Psychol Psychiatry* 2018;59(10):1105–1113). The other two studies did not find childhood symptoms in the majority of the teen-onset cases (67%–87%), although one of them found high rates of childhood conduct disorder (29%) and oppositional defiant disorder (23%) in the teen-onset cases (Agnew-Blais JC et al, *JAMA Psychiatry* 2016;73(7):713–720; Caye A et al, *JAMA Psychiatry* 2016;73(7):705–712).

In summary, ADHD can start in the teenage years, but if you look hard enough, you'll probably see some traces of the disorder in the patient's childhood.

Adult-onset ADHD

In 2015, a study from Dunedin, New Zealand made headlines with the claim that the first evidence of adult-onset ADHD had been found. The study prospectively followed over 1,000 children from infancy to middle age. It compared ADHD at two time points: ages 5–7 and age 38. Childhood diagnoses were confirmed by parents and teachers, and adult diagnoses were made with structured interviews by raters who were blind to childhood diagnoses (Moffitt TE et al, *Am J Psychiatry* 2015;172(10):967–977).

The prevalence of ADHD in the Dunedin study corresponded to what we would expect: 6% in children and 3% in adults. But when the investigators looked at which individuals received the diagnosis, the results were stunning—there was virtually no overlap between children who were diagnosed with ADHD and adults who received the diagnosis.

Where did the new ADHD come from? It did not seem to develop gradually out of sub-threshold symptoms; 90% of the later-onset ADHD cases did not have ADHD symptoms as children. On the other hand, 30% of them had childhood histories of conduct disorder, so it may have been due to an ADHD-like pathology that was expressed differently in childhood.

Less clear is when this "adult-onset" ADHD began. The researchers did not ask the 38-year-olds that question, and did not interview them in their late childhood or teen years. While intriguing, these results fall short of proving "adult-onset" ADHD.

Potential causes

When ADHD begins after age 12, we are much less certain of what we're dealing with, especially if it starts in adulthood. There are at least 3 possibilities to keep in mind:

1. **Late-onset ADHD develops out of sub-syndromal childhood symptoms.** This is suggested by some, but not all, of the studies.
2. **Late-onset ADHD was present in childhood but the symptoms were forgotten.** Recall of childhood symptoms is notoriously unreliable, which is why these studies used a prospective design to get around that problem. In practice, however, we don't have that luxury, and many patients with valid adult ADHD simply don't recall their childhood symptoms. Sometimes it's suggested that the childhood symptoms were masked by a high IQ or supportive family, and while that makes intuitive sense, the prospective studies

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Adult ADHD: What Else Could It Be?

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

In this issue, we tackle one of the vexing problems in outpatient psychiatry: adults who present with ADHD. Some of these patients can trace their symptoms back to their childhood or teenage years, and these patients may indeed have legitimate ADHD. However, ADHD symptoms are hard to pin down. They change significantly through a person's lifespan, and many adult psychiatric disorders can mimic the symptoms of ADHD.

Clinical approach to adult ADHD symptoms

How should you approach the diagnosis of an adult who complains of distractibility and poor focus? While ADHD may be a possibility, I suggest you start by ruling out other potential causes, which I have listed in the table at right.

One overlap that's particularly difficult to untangle is ADHD and bipolar disorder. About 1 in 5 patients with bipolar disorder do have genuine ADHD. In those cases, the ADHD symptoms can be traced back to childhood and remain stable between the bipolar episodes. Outside of that overlap, cognitive problems are common in bipolar disorder. They often persist after the mood episodes resolve, and worsen as the number of episodes increases.

Of course, in psychiatry (as in life) nothing is simple, and these alternative explanations of ADHD symptoms are sometimes the products of underlying ADHD. For example, substance abuse and head injuries can cause an ADHD-like picture, but ADHD is also a potential cause of accidents and impulsivity. Sleep deprivation causes ADHD symptoms, but insomnia, restless legs syndrome, and procrastination-induced all-nighters are more common in ADHD. Obesity impairs cognitive function through effects on the hippocampus and prefrontal cortex, but ADHD is a risk factor for obesity (Cortese S et al, *Am J Psychiatry* 2016;173(1):34–43).

Alternative Causes of "ADHD" Symptoms in Adults	
Medical disorders	Thyroid disorder, inflammatory illnesses (HIV, Lyme disease), small vessel ischemic disease, sleep apnea, menopause, recent chemotherapy, toxin exposure, prenatal cocaine exposure.
Traumatic brain injury	Look for repeated, mild concussions from sports injuries or other traumas.
Age-related cognitive decline	Typically begins after age 45. Memory problems predominate and hyperactive symptoms are lacking.
Medication effects	Anticholinergics, anticonvulsants, chronic benzo use, substance abuse.
Sleep deprivation	The cognitive effects of sleep deprivation improve with stimulants, but the health effects do not.
Depression and bipolar disorder	Cognitive problems are common during mood episodes, and they can persist even after the episodes resolve. Cognitive problems from a mood disorder tend to worsen as the episodes recur. In contrast, cognitive problems due to ADHD are stable and present from an early age.
Personality disorders	Borderline personality disorder and ADHD can be genuinely comorbid, but borderline patients have a greater risk of aggression and paranoia on stimulants. Patients with perfectionistic personality styles may over-emphasize mild cognitive problems and self-report ADHD.
Other	Autism, learning disorders, generalized anxiety disorder, and childhood neglect can all present as ADHD.

Adult-Onset ADHD

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found the opposite pattern. Late-onset cases had slightly lower IQs and more psychosocial problems in their homes than healthy controls.

3. **Late-onset ADHD is simply misdiagnosis of another psychiatric disorder.** The 4 studies above ruled out other psychiatric causes of the ADHD symptoms (except personality disorders), but a smaller study found strong support for the misdiagnosis theory. They followed 239 children from ages 10 to 25 with regular assessments from parent, teacher, and self-reports along the way. None of the children had ADHD at the start of the study, and 17% developed ADHD after age 12. However, 95% of these late-onset cases could be attributed to substance use or other mental disorders (Sibley MH et al, *Am J Psychiatry* 2018;175(2):140–149). (See "Adult ADHD: What Else Could It Be?" above for more on those possibilities.)

Back to Alex. His symptoms began in his late teens, so based on these new studies, it's possible he has ADHD. His family history also points that way. After ruling out other causes of adult ADHD, we might consider starting an antidepressant with benefits in ADHD, like bupropion, or a stimulant. Alex has mild depression, but those symptoms might clear up as his functioning improves with stimulant treatment.

If using a stimulant, we'd need to watch Alex carefully because we don't have confirmation that his ADHD began before age 12. If he tries taking a stimulant and the benefits keep wearing off, we should reconsider the diagnosis instead of raising the dose beyond the maximum in the PDR.

TCPR VERDICT: Teenage-onset ADHD does exist, although many of these patients had behavioral problems or milder symptoms of ADHD in their childhood years. Adult-onset ADHD, however, has not been confirmed. When patients present with ADHD symptoms that began after age 12, look carefully for other causes, and monitor closely if stimulants are used.

Expert Interview

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their doses and breadth of ingredients, which is how they exert a therapeutic effect (see "Micronutrients Discussed by Dr. Rucklidge" table on page 5).

TCPR: What did you see in the ADHD studies?

Dr. Rucklidge: We've done two randomized, placebo-controlled trials in ADHD, one in children (n = 93) and one in adults (n = 80). None of them were taking medications for ADHD, and we treated them with either a micronutrient formula or placebo. The specific formulas we used were EMPowerplus in the adult study and Daily Essential Nutrients in the child study. In the children, we saw improvement in emotional regulation, aggression, inattention, and general functioning after 10 weeks. Compared to placebo, the micronutrients had a moderate effect size, and benefits were observed across patient, parent, teacher, and clinician report. In the adult trial, we saw improvements in the patient-rated and observer-rated symptoms, but the clinician-rated measures were only positive on the Global Assessment of Functioning (GAF), which speaks to what these micronutrients are doing. They are not specific treatments for ADHD. Rather, they have a broader effect on mental health (Rucklidge JJ et al, *J Child Psychol Psychiatry* 2018;59(3):232–246; Rucklidge JJ et al, *Br J Psychiatry* 2014;204:306–315).

"Micronutrients help emotional dysregulation. We see symptoms improve with micronutrients, and we see related improvements in the ability to self-regulate. Patients sleep better, are better able to cope with stress, and—anecdotally—are less likely to turn to alcohol, drugs, or cigarettes."

Julia Rucklidge, PhD

TCPR: Do you see micronutrients as treatments for specific disorders? Or do they improve mental health more broadly in the way that social supports, exercise, and good sleep do?

Dr. Rucklidge: I think they are improving mental health more broadly. They seem to have similar effects regardless of the population that was studied. To sum up dozens of controlled studies, I'd say that micronutrients help emotional dysregulation.

TCPR: What does emotional dysregulation look like in real life?

Dr. Rucklidge: Volatile, irritable, anxious, reactive. People with emotional dysregulation might meet criteria for different disorders in the DSM. You're walking on eggshells with them because their mood can change so quickly. They might be aggressive; it might express itself in temper tantrums in children. You might end up with a lot of anxiety as a consequence of being emotionally dysregulated. We see all those symptoms improve with micronutrients, and we see related improvements in patients' ability to self-regulate. They sleep better, are better able to cope with stress, and—anecdotally—are less likely to turn to alcohol, drugs, or cigarettes.

TCPR: So micronutrients may help nonspecific symptoms, but they were also studied in specific populations. Which populations have they been studied in?

Dr. Rucklidge: There are randomized controlled trials in juvenile delinquents, school children, healthy adults, and prisoners that generally confirm this effect on emotional regulation. There are two studies in autism where micronutrients improved hyperactivity, tantrums, and receptive language (Adams JB et al, *BMC Pediatr* 2011;11:111). We don't have positive studies in bipolar disorder and schizophrenia, although a few specific nutrients have positive results in those populations, mainly omega-3s, N-acetylcysteine, vitamin D, and B vitamins (Balanzá Martínez V, *Actas Esp Psiquiatr* 2017;45:16–25; Fusar-Poli L et al, *J Affect Disord* 2019;252:334–349).

TCPR: Are there positive studies in depression?

Dr. Rucklidge: Yes, there is one on EnLyte, a branded micronutrient that has been cleared by the FDA as a medical food. EnLyte contains zinc, methylfolate, and B vitamins. In that study, it was the depressive symptoms themselves that improved, and the effect size was large (0.9). Importantly, the study only enrolled depressed patients with abnormalities at the methylenetetrahydrofolate reductase (MTHFR) gene, which is involved in folate metabolism. The study was large (n = 330), double blinded, and placebo controlled (Mech AW and Farah A, *J Clin Psychiatry* 2016;77(5):668–671). We are currently conducting a large randomized controlled trial of Daily Essential Nutrients in depression.

TCPR: Which age groups have the best response?

Dr. Rucklidge: There doesn't seem to be an age effect. In our ADHD studies, we saw pretty much the same effects in adults and children. Older people also do well on micronutrients. So far, we don't really know who is going to respond. We've looked into biomarkers like the MTHFR gene, inflammatory markers, and even direct serum measurements of vitamins and other micronutrients. But none of these reliably predict response.

TCPR: So you don't need to have a micronutrient deficiency for these to work?

Dr. Rucklidge: Well, at least not from the point of view of the clinical measures we've looked at. We've measured levels that are commonly available, like B12, folate, copper, zinc, and vitamin D. In our research, people who have a deficiency in those nutrients are just as likely to respond as those who have normal levels. But there's a caveat there. Lab tests only tell us about population averages. They don't tell us if an individual's levels are meeting the person's needs.

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Expert Interview

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Someone might have a greater need for zinc, for example, because of genetic differences. Another person might have "low" levels that are plenty sufficient for that person's needs. I'm being a little speculative here as we don't have enough research to prove that (Rucklidge JJ et al, *Prog Neuropsychopharmacol Biol Psychiatry* 2014;50:163–171).

TCPR: What about side effects and risks?

Dr. Rucklidge: You might see stomachaches or headaches, but generally micronutrients are well tolerated and safe. In our controlled studies, we saw similar rates of side effects for placebo and micronutrients. We also have long-term extension studies, where micronutrients continued to be effective in 85% of patients and remained well tolerated (average follow-up 2.7 years). There are rare cases where a micronutrient may cause problems—for example, someone with hemochromatosis should not take iron, and a person with Wilson's disease should not supplement with copper.

TCPR: If psychiatrists want to recommend micronutrients, how do they choose a product?

Dr. Rucklidge: Well, first let me say I have not received any money from companies that make these products, and I don't endorse any particular brands. But I can tell you which brands have the most research behind them: Daily Essential Nutrients and EMPowerplus. Newer products are moving toward methylated vitamins, like methylfolate instead of folic acid, or methylated B12, which may be more effective for some patients. Daily Essential Nutrients are methylated, and EMPowerplus has a methylated version as well. *(Ed. note: For more on methylated folate, see* TCPR, *August 2019.)*

TCPR: Your recent studies have utilized Daily Essential Nutrients. Did you do those without any support from the manufacturer?

Dr. Rucklidge: The companies that make Daily Essential Nutrients and EMPowerplus seem to have a general policy that they'll provide free pills and matching placebo for anyone who wants to do a study. They don't ask any questions and play no role in the development of the studies. They have only one caveat: The study has to be approved by an ethics board. So that's the extent of their involvement. The financial backing for this research has come from charitable donations, grants, and academic awards.

TCPR: Each of these products has 20–30 ingredients in them. How did the manufacturers decide on the ingredients?

Dr. Rucklidge: The original formulas were developed in the 1990s by families in Alberta, Canada. These parents were struggling with mental disorders in their children that didn't respond to conventional treatments. So they looked in other directions, in this case farming. Farmers have known for centuries that when their animals get irritable and start biting each other, the animals' irritability gets better when they're fed a broad spectrum of nutrients. The families started from there and added individual nutrients into the mix that have positive studies for mental health, like inositol, choline, and N-acetylcysteine.

TCPR: There are good studies on those individual nutrients. What is the advantage to taking them all together in a micronutrient pill?

Dr. Rucklidge: The thinking is that no one nutrient is special. You need them all in combination. It's the same reason that we need variety in our diets. We tested this idea out in a study of healthy adults who were impacted by a natural disaster. We compared micronutrients to a single nutrient (vitamin D) or a few nutrients (B-complex

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Micronutrients Discussed by Dr. Rucklidge

Brand	Daily Dose	Vitamins	Minerals	Other
Daily Essential Nutrients (www.hardynutritionals.com)	4 caps TID ($4.32/day) Start with 1 TID and increase by 1 every 2 days; raise slower if there are any tolerability problems A lower dose (4 caps/day) is recommended for general health	A, B1, B2, B3, B6, B7, B12, B5, B9, C, D, E, K	Calcium, iron, phosphorus, iodine, magnesium, zinc, selenium, copper, nickel, boron, manganese, chromium, molybdenum, potassium, vanadium, trace lithium	Choline, inositol, grapeseed extract, methionine, ginkgo, alpha-lipoic acid, acetyl-L-carnitine, N-acetylcysteine
EMPowerplus Advanced (www.truehope.com)	4 caps BID ($4.68/day) or 8 tabs BID ($5.60/day) Start with 1 cap BID (or 2 tabs BID) and increase by 1 cap (or 2 tabs) every 2 days; raise slower if there are any tolerability problems A lower dose (2 caps/day or 4 tabs/day) is recommended for general health	Same as above (without vitamin K)	Same as above (without lithium)	Choline, inositol, grapeseed extract, methionine, ginkgo, alpha-lipoic acid, acetyl-L-carnitine, N-acetylcysteine, phenylalanine, citrus bioflavonoids, L-glutamine, germanium sesquioxide
EnLyte (www.enlyterx.com)	1 8.73 mg soft gel QD ($1.75/day at www.enlyterx.com, or may be covered by insurance)	B1, B2, B3, B6, B9 (as methylfolate, folate, and folinic acid), B12	Iron, magnesium, zinc	*Cofactors:* flavin adenine dinucleotide, nicotinamide adenine dinucleotide, trimethylglycine *Phospholipids:* omega-3, phosphatidylserine

Stimulants as Cognitive Enhancers

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

Depending on your practice setting, you are likely to encounter adults who seek stimulants for various "non-medical" uses, from cognitive enhancement to recreational abuse to outright diversion.

Abuse and diversion are easier to detect these days with the controlled substance databases available in most states. Abuse of stimulants is relatively rare. Over 90% of recreational stimulant users do not meet DSM-5 criteria for abuse (Arria AM and DuPont RL, *Am J Psychiatry* 2018;175(8):707–708). Instead, many are using them to enhance their cognitive performance. This kind of "cosmetic psychopharmacology" is so common in the college years (20%–30% of students) that stimulant prescriptions are banned or severely restricted at many college mental health centers.

High-achieving adults are also at risk. When the journal *Nature* polled its readers anonymously, 1 in 5 were taking non-prescribed stimulants to enhance their focus, memory, and concentration (Maher B, *Nature* 2008;452(7188):674–675). Elvis Presley, John F. Kennedy, and Hugh Hefner all took stimulants to enhance their performance. Kennedy and Hefner stopped when their associates noticed signs of irritability and paranoia, but the King's use went largely unchecked and may have contributed to his erratic behavior in the 1970s.

Contrary to popular belief, stimulants do not always improve mental functioning in healthy individuals. Overall, meta-analyses have failed to support a significant improvement, although they do appear to work in situations that require sustained attention to boring, repetitive tasks. Stimulants can also reverse some of the effects of sleep deprivation, but a new placebo-controlled study suggests they may impair cognition by disrupting sleep the next day. A single dose of dextroamphetamine 20 mg was enough to impair sleep and, on the day after, working memory, even when given as an instant release in the morning (Tselha T et al, *Behav Brain Res* 2019;370:111940).

More concerning are the long-term risks of stimulants when used outside of ADHD. Their abuse potential and cardiovascular risks are well known. Rarely, they can cause psychosis, and in high doses they have neurotoxic effects, causing apoptosis (ie, cell death) in the brain. Both of these risks are greater with the amphetamines (eg, Adderall and Vyvanse) than the methylphenidates (eg, Ritalin, Focalin, Concerta) (He W et al, *Neurotox Res* 2018;34(2):233–240; Moran LV et al, *N Engl J Med* 2019;380(12):1128–1138).

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Expert Interview

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vitamins). It was a small randomized trial (n = 56) with no placebo. When compared to the other vitamins, improvements were significantly greater with the micronutrients on measures of anxiety and stress (Kaplan BJ et al, *Psychiatry Res* 2015;228(3):373–379).

TCPR: Was the goal to prevent PTSD with micronutrients?

Dr. Rucklidge: Yes. This was in the summer of 2013 when there was severe flooding in Alberta, New Zealand. A lot of things fall apart when a natural disaster strikes, including food and nutrition, so we thought that micronutrients might be particularly helpful in this setting. We've done similar interventions after the earthquakes in 2010 and the mosque shooting last spring. The results were positive, but unlike the flood study, they weren't randomized.

TCPR: Are there other ingredients in these products besides minerals and vitamins?

Dr. Rucklidge: Over the years, manufacturers have added in small doses of ingredients that I wouldn't classify as micronutrients, like ginkgo or grapeseed extract. Those are few in number and small in amount, but they do make it hard to say definitively that it's the micronutrients that are making the difference.

TCPR: I understand that the "nutrient" in micronutrients refers to minerals, vitamins, and amino acids. What does "micro" mean?

Dr. Rucklidge: We call them "micro" nutrients because they are much smaller than macronutrients: fats, carbohydrates, and proteins. Micronutrients are part of a healthy diet, but much of the Western diet is depleted of micronutrients. For some, that doesn't matter as much and it's not going to affect their mental health, but other patients are more vulnerable.

TCPR: Could patients get the same benefits by changing their diet?

Dr. Rucklidge: Yes. Food is where I go first. I recommend a diet that is low in processed foods and high in fruits and vegetables and healthy fats from nuts, seeds, and fish. Sometimes that works, but there are reasons why dietary change might not work. One is environmental. Society favors food that grows quickly, and when plants grow fast, they don't take up as many nutrients from the soil. We don't remineralize the soil, and instead we use herbicides like Roundup that leach minerals. Then there's storage and transport. Once an apple is picked from a tree, the nutrient content decreases, and continues to decrease as it is shipped. When the food arrives in our kitchen, we cook it, and that can further deplete the nutrients. Finally, differences in genetics and the gut microbiome influence how available those nutrients are in the body after the food is eaten.

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

A Practical Guide to Light Therapy

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

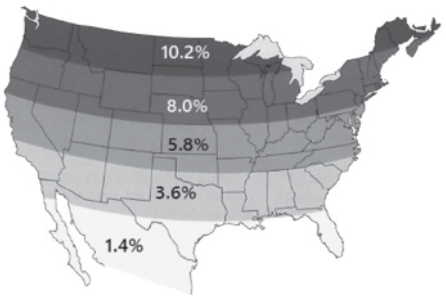
Outdoor living, morning light, evening darkness, and regular rhythms of sleep and waking all have one thing in common: They prevent depression. That's the conclusion of many large epidemiologic studies, but for people who work indoors and wake up to dark winter mornings, this isn't good news (Asai Y et al, *J Affect Disord* 2018;241:235–240). Here's where light therapy fits in.

Light therapy was discovered at the NIMH in the early 1980s. It has since become a standard treatment for winter depression, with over 100 clinical trials and an effect size that compares favorably to medication: 0.5–0.8 (Mårtensson B et al, *J Affect Disord* 2015;182:1–7). It also works in non-seasonal depression, possibly because indoor living affords limited access to bright light. Even the brightest indoor spaces (500 lux) are only half as bright as an overcast day (1,000 lux) and far darker than a sunny one (10,000–30,000 lux).

Other photosensitive disorders that show promise with light therapy include ADHD, bulimia, dementia, Parkinson's disease, and sexual dysfunction in men, as well as circadian rhythm disorders such as shift work, jet lag, and insomnia due to delayed sleep phase disorder (aka extreme night owls) (Botanov Y and Ilardi SS, *PLoS One* 2013;8:e75893).

To use this therapy, you'll need to know a few basics, starting with how to recommend the right device.

Rates of Winter Depression in U.S.



Selecting a light box

The more popular a light box is, the less likely it is to work. That's because the qualities that make a light box commercially attractive—slimness, portability, and unobtrusiveness—will also keep it from giving off enough light to treat depression. Here's what is required: a large screen (at least 12 x 17 inches) that hangs over the head and gives off intense light (at least 2,000 lux; 10,000 lux is ideal) in the white spectrum. "Full spectrum" and blue lamps do not have good evidence for better efficacy, but they do cause problematic glare.

To simplify this process, a group of researchers has stepped in with specific product recommendations at www.cet.org. Currently they recommend Northern Light Technology's BOXelite OS ($180). Another good option that has been used in clinical trials is Carex's Day-Light Classic or Classic Plus ($100–$140; the regular Classic has folding stands). The bulbs on a light box will lose a little of their therapeutic intensity over time, even if they continue to appear bright, so they work best when replaced every 2–3 years. Replacement bulbs are around $20 on Amazon (BOXelite uses Philips PL-L 36W or Sylvania FT36DL; Carex uses DL930 bulbs).

Timing the treatment

It's not just the quantity of light, but the timing that matters. Light therapy works in part by setting the biological clock, and morning light has the most potent effect on that circadian system. The "sweet spot" for light therapy is generally between 5:00 a.m. and 8:00 a.m. and depends on whether the patient is a morning person (closer to 5:00 a.m. is ideal) or a night owl (closer to 8:00 a.m. is ideal). Michael Terman's group at Columbia University developed a self-report

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Light Therapy in Bipolar Disorder

Winter depression is common in bipolar disorder, but in spring the sudden increase in sunlight can cause mania and mixed states. Likewise, case reports suggest that light therapy can trigger mania, especially if it's titrated too quickly or delivered in the early morning. Manic symptoms are less likely with midday treatment (12:00–2:00 p.m.), and this strategy worked well in a randomized controlled trial in non-seasonal bipolar depression. The light was titrated slowly, starting with 15 minutes a day and increasing by 15 minutes each week toward a target of 1 hour (Sit DK et al, *Am J Psychiatry* 2018;175:131–139).

If midday treatment is impractical, morning light might be safe in bipolar. It worked well without manic induction in 2 controlled trials, and in a literature review, it was not associated with manic switching in 799 patients with bipolar disorder (Benedetti F, *Psychiatry Res* 2018;261:351–356). However, I'd stick with the midday protocol if the patient has bipolar I disorder or a recent problem with manic or mixed symptoms (in bipolar terms, recent means the past 6 months). If mixed symptoms emerge during light therapy, decrease the time under the light box, move it to midday, or stop the treatment entirely. Or, you could try dark therapy.

Dark therapy is the corollary of light therapy. It has mood-stabilizing effects and can be used in the evenings after morning light therapy to prevent mania. Dark therapy requires patients to stay in pitch darkness or wear blue light–blocking glasses from early evening (around 6:00 or 8:00 p.m.) to morning (8:00 a.m.) (see *TCPR,* February 2019). Again, timing is the issue with light and darkness. Dark mornings can cause depression, but darkness at night improves depression and mania based on large epidemiologic and small clinical trials (Obayashi K et al, *Am J Epidemiol* 2018;187(3):427–434).

A Practical Guide to Light Therapy
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scale to predict the optimal start time (the Morningness-Eveningness Questionnaire or AutoMEQ at www.cet.org/assessment/confidential-self-assessments).

Most patients with depression need 30–60 minutes of light therapy per day; mild cases may need as little as 15 minutes. Patients should start to see improvement within 1–2 weeks. If they have not recovered after 4 weeks, try to increase the duration (eg, up to 2 hours). Patients with a strong seasonal pattern should start the therapy preventatively 2 weeks before their winter episodes typically begin. Light therapy can also augment antidepressants, both in seasonal and non-seasonal depression, with an effect size that compares well to other augmentation strategies (0.5) (Penders TM et al, *Prim Care Companion CNS Disord* 2016;18(5). doi: 10.4088/PCC.15r01906).

Positioning the box

Patients should sit with the box slightly tilted at a 30° angle over their head. They can read, eat, use a computer, or meditate under the light, but should avoid looking directly into it for the same reasons they shouldn't stare at the sun. They can wear glasses as long as they don't have transition, blue light–blocking, or tinted lenses. The intensity of the light falls exponentially with distance, so their head should stay 10–14 inches from the screen, depending on the light box model.

Troubleshooting

Many patients are skeptical of light therapy. I'll emphasize that it's as effective as an antidepressant and alters neurotransmitters like serotonin, dopamine, and melatonin. Others accept that light is beneficial, but think that a sunroom or bright reading lamp will suffice. All of those are helpful, but they emit an intensity of light that was used as a placebo in the light therapy trials (300–1,000 lux). On the other hand, morning aerobics or a 1-hour outdoor walk in the winter has good evidence of effectiveness in seasonal depression.

Timing is another obstacle. If early morning is not practical, patients can still benefit by using the light box later in the day, as long as it's not past 2:00 p.m. After that time, light therapy will actually flip the biological clock in the wrong direction, possibly resulting in depression, insomnia, and mania. Patients who have difficulty getting out of bed to start light therapy can benefit from a dawn simulator, which improves wakefulness and energy in the morning (see *TCPR,* February 2019).

Safety

Light therapy is well tolerated. Headaches, eye strain, and mild nausea are the most common adverse effects. The main risk is the exposure to high-intensity light, which can damage the skin and eyes. Recommended boxes have a diffusion screen that filters out ultraviolet light, the most harmful ray. Blue light, which lies next to the ultraviolet spectrum, will still pass through and may pose a problem for patients who have retinal disease or take photosensitizing medications like lamotrigine, antipsychotics, or tricyclics. Reports of actual problems are very rare, but patients should consult with their ophthalmologist if this is a concern (Brouwer A et al, *Acta Psychiatr Scand* 2017;136:534–548).

TCPR VERDICT: Light therapy is a top recommendation for seasonal depression and can work in non-seasonal and bipolar depressions as well. It's an investment of time (30–60 minutes a day), but it causes few side effects and has benefits that compare favorably to those of antidepressants.

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News of Note

Meet the First H_3 Antagonist

On August 15, 2019, pitolisant (Wakix) received FDA approval for narcolepsy, making it the first release of a histamine-3 (H_3) antagonist.

Unlike other narcolepsy medications, pitolisant is not a controlled substance and lacks abuse potential. Those other options for narcolepsy are the stimulants (methylphenidate and amphetamine), the modafinils, sodium oxybate (Xyrem), and the newly released solriamfetol (Sunosi), a dopamine and norepinephrine reuptake inhibitor that we reviewed in the June/July issue of *TCPR*. Pitolisant has been compared to modafinil in 2 head-to-head trials, where pitolisant had similar efficacy but better tolerability (total n = 260) (Romigi A et al, *Drug Des Devel Ther* 2018;12:2665–2675).

Pitolisant's main side effects are insomnia, headache, nausea, and anxiety. As a weak CYP3A4 inducer, it may decrease oral contraceptives.

The H_3 histamine receptor is mainly found in the brain, where it regulates wakefulness, appetite, and memory. Pitolisant blocks the H_3 receptor, and this blockade causes downstream effects of increased dopamine and acetylcholine in the prefrontal cortex. That profile has led to investigations of pitolisant in ADHD, dementia, obesity, and cognitive symptoms of schizophrenia. So far the results have not proved as promising as the narcolepsy findings, but most of those trials are incomplete or unpublished. It's an intriguing mechanism, and we expect to learn more about its psychiatric effects in the future (Syed YY, *Drugs* 2016;76(13):1313–1318).

—Chris Aiken, MD.

An Antipsychotic Patch

Asenapine (Saphris) is now available as a transdermal patch, Secuado. The patch showed efficacy in a large 6-week, double-blind, placebo-controlled, fixed-dose study in 616 adult patients with schizophrenia.

Transdermal medications are thought to reduce side effects by avoiding "first-pass" metabolism in the GI tract. This is unlikely to be an advantage

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News of Note

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for Secuado, however, because the sublingual form of asenapine (Saphris) already avoids the first-pass effect by absorbing through the buccal membrane. Compared to placebo, Secuado's side effect profile looks identical to Saphris, except that it adds one more: skin irritation (15%). Still, some patients may prefer it to Saphris, which is notorious for its unpleasant taste that is not always masked by its black cherry flavoring.

The main difference between Saphris and Secuado is in their pharmacokinetics. Saphris comes on fast, peaking within an hour, while Secuado takes 12–24 hours to reach peak levels. Peak levels are associated with side effects, however, not efficacy. Some patients do better with lower levels spread out over a long time (Secuado), while others prefer the rapid up and rapid down of Saphris. In other words, Secuado is to Saphris as Seroquel XR is to Seroquel IR.

Secuado's advantages over Saphris are dampened when Saphris is given as a single nightly dose. This minimizes fatigue by concentrating the side effects in the evening. Although it's recommended to divide Saphris twice daily, there is little reason to do so either in schizophrenia or bipolar disorder. Antipsychotics can be given in a single daily dose without loss of efficacy, according to 4 randomized controlled trials (Takeuchi H et al, *J Clin Psychiatry* 2014;75(5):506–511). That is true for antipsychotics with short half-lives like perphenazine and clozapine, and makes even more sense with the 24-hour half-life of Saphris.

Secuado and Saphris have never been directly compared, but industry-sponsored papers touting the benefits of the transdermal form are already on the march (Citrome L et al, *J Clin Psychiatry* 2019;80(4)). *Caution:* These papers draw their arguments from transdermal systems designed for other diagnoses like ADHD and dementia. There the comparison is an oral medication given twice a day, not a sublingual one given all at night. Secuado may be right for patients whose side effects are tied to asenapine's peak plasma levels. Otherwise, Saphris is the better choice, particularly after December 2020 when it is expected to go generic.

—Chris Aiken, MD.

Secuado Patch vs Saphris Sublingual

	Secuado	Saphris
Dose conversion	3.8 mg/day	10 mg/day
	5.7 mg/day	15 mg/day
	7.6 mg/day	20 mg/day
Unique side effects	Skin irritation (15%)	Unpleasant taste
Pharmacokinetics	Slower Tmax (12–24 hrs), similar half-life (30 hrs); same drug interactions as Saphris	Faster Tmax (1 hr), similar half-life (24 hrs)
Advantages	Transdermal patches preferred by some patients and families and may increase adherence	The rapid onset means that side effects like fatigue can be minimized by taking the entire dose at night
Disadvantages	Absorption is decreased by oily, hairy skin, and increased by heat	Absorption is significantly decreased if patients eat or drink within 10 minutes after taking it; serum levels are mildly reduced (10%–20%) when a large meal is eaten 30 minutes before or up to 4 hours after the dose
Cost	Unknown	$600/month; goes generic December 2020

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Research Updates IN PSYCHIATRY

ANXIETY

Pharmacology for GAD: Complex Choices

REVIEW OF: Slee A et al, *Lancet* 2019;393(10173):768–777

STUDY TYPE: Network meta-analysis

With over 2 dozen choices, how do we pick a medication for generalized anxiety disorder (GAD)? The authors of this network meta-analysis sought to answer this question.

Network meta-analysis allows researchers to gauge treatments that haven't been directly compared in head-to-head studies. If drug A works better than drug B and B works better than C, then the network meta-analysis concludes that A is likely to work better than C, even though A and C have never been directly compared.

The investigators selected 89 trials of 25 drugs studied in over 25,000 patients. The primary outcome was change in the Hamilton Rating Scale for Anxiety (HAM-A). Trial length varied from 4 to 26 weeks.

Surprisingly, quetiapine XR was the most efficacious among the medications with large sample sizes. However, its benefit was modest, with a reduction of 3.6 points on the HAM-A compared to placebo (150–300 mg per night, as

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Research Updates IN PSYCHIATRY

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monotherapy). Quetiapine XR was poorly tolerated with a high discontinuation rate (odds ratio 1.44). The following drugs were well tolerated and are listed in order of efficacy: duloxetine, pregabalin, venlafaxine XR, and escitalopram.

The 4 benzodiazepines were studied as a class, not as individual drugs. Patients quit benzodiazepines much more often than placebo (odds ratio 1.43), although the reasons for discontinuation were not explored.

Studies were excluded if the patients had psychiatric comorbidities other than depression, which means the subjects might have been significantly less ill than the patients we see in routine practice.

One-third of the trials were not placebo controlled, and a fairly large number of them had limited quality. However, a sensitivity analysis concluded that these deficiencies did not significantly distort the results.

Although the meta-analysis did not analyze the data according to the quality of the studies, dose, or duration of treatment, *TCPR* has analyzed these issues by drilling down on the appendix and the original studies. The studies of pregabalin were all of lower quality. The studies of duloxetine were of the highest quality, followed by escitalopram and venlafaxine XR. For duloxetine, venlafaxine, and escitalopram, high doses (eg, duloxetine 120 mg) were no more efficacious than medium doses (eg, duloxetine 60 mg). Of these 3 antidepressants, only venlafaxine XR was studied for more than 12 weeks, and those studies demonstrated greater efficacy than shorter studies, suggesting that its benefits may build over time.

TCPR'S TAKE

In GAD, duloxetine stands out for its efficacy, safety, and the quality of its studies. This antidepressant has FDA approval in childhood GAD as well. It may take a few months to see the full effects of antidepressants in GAD, and medium doses are as likely to work as higher ones. Quetiapine XR is one of the more effective medications for GAD, but it has major safety and tolerability issues that caused the FDA to withhold its approval in 2009.

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

For an in-depth look at generalized anxiety disorder and its cousin, neuroticism, listen to our 4-part podcast series, premiering in November. Search for "Carlat" on your podcast store.

ANOREXIA NERVOSA

Olanzapine for Anorexia Nervosa

REVIEW OF: Attia E et al, *Am J Psychiatry* 2019;176(6):449–456

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

Antipsychotics have been tried in anorexia since 1960, but their success has been mixed and often outweighed by their risks. Seven controlled trials have tested atypical antipsychotics in anorexia, and although most were positive, their pooled benefits were too small to be detected in a meta-analysis (Dodd M et al, *Psychother Psychosom* 2015,84(2):110–116). That leaves us with an uncertainty that is best answered by a larger controlled trial, which is where this new research comes in.

In this randomized placebo-controlled trial, researchers studied the effects of olanzapine on change in body weight and obsessionality in adult outpatients (n = 152) with anorexia nervosa for 16 weeks. Nearly all patients were female (96%) and most were taking psychotropics (41%, mainly antidepressants). Average BMI was 17 and Yale-Brown Obsessive Compulsive Scale (YBOCS) was 16.5 (moderate severity). Olanzapine was started at 2.5 mg/day x 2 weeks, titrated to 5 mg/day x 2 weeks, and then increased to 10 mg/day as tolerated (average final dose 7.8 mg/day). Primary outcome measures were (1) rate of change in body weight and (2) rate of change in obsessionality measured by the YBOCS.

Relative to placebo, the olanzapine group experienced a significant increase of 0.165 BMI points, which is approximately 1 pound per month over the 16 weeks. Relative to placebo, the olanzapine group did not see a benefit in obsessionality or cognitive symptoms of anorexia, and had significantly more concerns about body weight. Lab abnormalities and hospitalization rates did not differ between the groups.

This study's strengths include the large sample size and enrollment of diverse patients with various comorbidities that are more reflective of outpatient practice. The sample size is almost as large as all the past atypical antipsychotic studies of anorexia combined. The study's main weaknesses include the large dropout rate (45%) and a duration that was probably not long enough to detect lab abnormality differences. On the other hand, the dropout rate was similar for olanzapine and placebo, and the data was analyzed on an intent-to-treat basis.

TCPR'S TAKE

Despite a positive result, these modest gains in weight do not inspire a ringing endorsement of olanzapine for anorexia. The study can't tell us whether that weight gain was due to a therapeutic effect on anorexia or to olanzapine's known metabolic effects, but the lack of improvement in other anorexia symptoms gives us pause. Reserve olanzapine for severe, treatment-resistant patients where weight restoration is essential, or for patients with anorexia who have comorbidities—like mood disorders—where olanzapine is indicated.

—Kristen Gardner, PharmD. Dr. Gardner has disclosed that she has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CME Post-Test

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For those seeking ABPN Self-Assessment (MOC) credit, a pre- and post-test must be taken online at http://thecarlatcmeinstitute.com/self-assessment/

Below are the questions for this month's CME/CE post-test. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Note: Learning Objectives (LO) are listed on page 1.

1. According to Dr. Rucklidge, which of the following statements is true about micronutrients? (LO #2)
   - [ ] a. Children respond more favorably to and experience less side effects from micronutrients than adults
   - [ ] b. Older adults experience more side effects from micronutrients compared to the other vitamins
   - [ ] c. Older adults respond more favorably to micronutrients than children
   - [ ] d. Micronutrients tend to be well tolerated in adults, older adults, and children

2. Which disorder is least likely to cause ADHD-type symptoms in adults? (LO #1)
   - [ ] a. Sleep apnea
   - [ ] b. Narcissistic personality disorder
   - [ ] c. Bipolar disorder
   - [ ] d. Borderline personality disorder

3. According to a 2019 study, which medications are first-line choices for generalized anxiety disorder in terms of patient efficacy and tolerability? (LO #4)
   - [ ] a. Duloxetine, paroxetine, pregabalin, and buspirone
   - [ ] b. Pregabalin, venlafaxine XR, citalopram, and buspirone
   - [ ] c. Duloxetine, pregabalin, venlafaxine XR, and escitalopram
   - [ ] d. Venlafaxine XR, escitalopram, fluoxide, and citalopram

4. According to a 2015 study, what percentage of the later-onset ADHD patients had ADHD symptoms as children? (LO #1)
   - [ ] a. 10%
   - [ ] b. 25%
   - [ ] c. 40%
   - [ ] d. 55%

5. Light therapy is an effective augmentation to antidepressant treatment for seasonal depression; however, its effectiveness has been minimal as an adjunct for non-seasonal depression. (LO #3)
   - [ ] a. True
   - [ ] b. False

6. Which of the following micronutrients is FDA approved as a medical food? (LO #2)
   - [ ] a. Hypericum
   - [ ] b. Epigallocatechin gallate (EGCG)
   - [ ] c. N-acetylcysteine
   - [ ] d. EnLyte

7. ADHD is a risk factor for obesity, while obesity can also result in ADHD-type symptoms. (LO #1)
   - [ ] a. True
   - [ ] b. False

8. Light therapy is most effective for seasonal depression when delivered at which time? (LO #3)
   - [ ] a. Morning
   - [ ] b. Afternoon
   - [ ] c. Evening
   - [ ] d. All times have equal effect

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In Brief: Antipsychotic Update

Outdoor activity, massage, and touch therapy ranked most effective for agitation in dementia. In a meta-analysis of 163 randomized controlled trials, nonpharmacologic interventions were more effective than antipsychotics for aggression and agitation in dementia (Watt JA, *Ann Intern Med* 2019 Oct 15).

Risperidone doesn't appear to cause fractures. Risperidone did not increase the risk of fractures any more than other antipsychotics in a cohort study of 116,000 patients who were given a new prescription of any antipsychotic and filled it at least twice. There had been theoretical concerns about fractures on risperidone because it has a high rate of elevated prolactin (80%–90%), which in turn raises the risk of osteopenia. These reassuring results are in line with earlier clinical studies (Clapham E et al, *Acta Psychiatr Scand* 2019 Sep 23).

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