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Chris Aiken, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Treatment-Resistant Depression

Learning Objectives

After reading these articles, you should be able to:

1. Describe recent pharmacologic and non-pharmacologic treatments for managing treatment-resistant depression.
2. Discuss behavioral techniques to assist patients with rumination.
3. Summarize some of the current research on psychiatric treatment.

Treatment-Resistant Depression: Some Introductory Tips

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

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

Treatment-resistant depression (TRD) has a fairly low barrier of entry. Failure of 2 full antidepressant trials—lasting 6 weeks at a minimally effective dose—is enough to qualify. In this month's issue of *TCPR*, we'll highlight pharmacologic advances that are underutilized and debunk a few that are unlikely to be effective for TRD. But first, we offer the following strategies to guide you in this work.

In Summary

- Treatment-resistant depression (TRD) is usually diagnosed following at least 2 failed, 6-week antidepressant trials.
- Diagnosing TRD should take into account several factors, among them ruling out bipolar disorder.
- Treating TRD can be challenging. Take care not to let the patient's hopelessness influence your reasoning, and don't give up; there are many options.

Rule out bipolar disorder

Nonresponse to antidepressants is not enough to diagnose bipolar disorder,

Continued on page 2

Q&A With the Expert

Understanding Depressive Rumination

Edward Watkins, PhD

Professor of Experimental and Applied Clinical Psychology at the University of Exeter, UK. Director of the Mood Disorders Centre and the Study of Maladaptive to Adaptive Repetitive Thought (SMART) Lab.

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

Editor's Note: We often come across patients who seem stuck in a repetitive, negative style of thinking that we call rumination. Rumination is often associated with depression or anxiety, and when severe, it can seem akin to psychosis. The symptoms are common to many disorders but diagnostic of none. Patients call it stewing, over-analyzing, or "stinkin' thinking." There's no specific medication for rumination, though treating the underlying condition can help. Psychotherapy looks more promising, and Dr. Watkins has developed a new form of CBT that targets rumination. Many of his ideas involve straightforward behavioral strategies, and I've found they translate well into the brief therapy sessions that often accompany a medication visit.

TCPR: Why is it important to address rumination in patients with depression?

Dr. Watkins: Treating rumination is likely to achieve fuller and more lasting remission from depression. People who ruminate are more likely to get stuck in depression, less likely to benefit from treatments, and more likely to experience future episodes of depression (Watkins ER et al, *Br J Psychiatry* 2011;199(4):317–322).

Continued on page 3

Treatment-Resistant Depression: Some Introductory Tips

Continued from page 1

but it is a good reason to take a closer look: 40%–60% of TRD cases turn out to have a bipolar diagnosis after structured testing (Francesca MM et al, *Clin Pract Epidemiol Ment Health* 2014;10:42–47). Other signs pointing that way include the following:

- Family history of bipolar disorder
- History of worsening on antidepressants
- Onset of depression in adolescence

Rescreen for hypomania with a structured interview (see moodtreatmentcenter.com/measurement), and dig deeper when patients give ambiguous answers such as, "Not really ... not anymore," or rationalizations such as, "I'm only hyper when I have a lot to do." Remind patients that hypomania may have been brief, felt normal, or happened long ago.

Patients often answer differently on paper, and the Bipolar Spectrum Diagnostic Scale (see moodtreatmentcenter.com/measurement) is good at detecting hypomania. Print a copy for a relative to complete and you may get an entirely different set of answers.

Look for depressive subtypes and comorbidities

Subtypes of depression can point the way toward better treatment, such as a light-box for seasonal depression or MAOIs for atypical features (see page 8 for more on MAOIs). Psychotherapy is often helpful for comorbidities, particularly personality disorders, OCD, addictions, eating disorders, and anxiety disorders. Some of those tend to be veiled in secrecy, such as OCD and addictions, and need a little more probing to diagnose.

Address physical health

Though they are rarely the sole cause of depression, medical problems are frequent contributors, particularly chronic pain, obesity, and inflammatory illnesses. Consult with the primary care physician, check labs, and—for sleep apnea—look for loud snoring, collar size ≥ 17 inches, age ≥ 50, BMI ≥ 35, hypertension, and fatigue. Possible labs to check include thyroid, LFTs, electrolytes, CBC, folate, B12, vitamin D, and testosterone (in men).

Consider pharmacogenetic testing

Pharmacogenetic testing may be useful if treatment resistance has been extensive, though its value is still being debated. While the evidence is mixed, patients who worsen on antidepressants may carry the short allele of the serotonin transporter gene. What's less controversial is that some patients are slow metabolizers (leading to side effects), whereas others are fast metabolizers (causing low serum levels of antidepressants). Research is ongoing to determine whether commercially available genetic tests are actually valuable for clinicians in the trenches.

Ask about adherence

Leading questions help here: "Most people don't take their medications as prescribed, and some don't take them at all. How many doses do you tend to miss each week?"

Measure your work

This tip may double your remission rates. In a 6-month study that randomized 120 patients to receive treatment

Continued on page 12

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Welcoming Our New Editor-in-Chief

We're pleased to introduce Chris Aiken, MD, as the new editor-in-chief of *The Carlat Psychiatry Report*. Dr. Aiken is a clinician, researcher, and writer. He is the director of the Mood Treatment Center in North Carolina, where he maintains a private practice combining medication and therapy along with evidence-based complementary and alternative treatments.

He has worked as a research assistant at the NIMH and a sub-investigator on clinical trials, and conducts research on a shoestring budget out of his private practice. Dr. Aiken completed medical school at Yale and psychiatric residency at Duke and Payne-Whitney Cornell, and serves as a clinical instructor in psychiatry at Wake Forest University. He is a regular columnist for *Psychiatric Times* and, along with Jim Phelps, the coauthor of the self-help book *Bipolar, Not So Much* (W.W. Norton, 2017). He has never given talks on behalf of the pharmaceutical industry, but is a frequent lecturer on psychiatric topics.

Dr. Aiken replaces Dr. Daniel Carlat as editor-in-chief, which will allow Dr. Carlat to play a larger role as publisher of *TCPR* and all other Carlat Publishing offerings.

Expert Interview

Continued from page 1

TCPR: So, when we say "rumination," are we talking about "worry," or are they different?

Dr. Watkins: Worry and rumination are very similar. Both involve repetitive thinking about negative events in an abstract and passive way, but they differ in content. Worry has a focus on future threats, while the focus of rumination is on the past, loss, and meanings for the self. Worry takes the form of "what if" questions, where people imagine negative consequences in their future. Meanwhile, rumination is characterized by questions such as, "Why did this happen? Why me? Why am I so depressed? Why does this always happen to me? Why can't I get better?"

TCPR: Can you give us a specific example of a patient who is having ruminative thoughts?

Dr. Watkins: Sure. Take a patient who has recently gone through a breakup. This patient, if ruminating, will likely focus on trying to understand why the relationship ended, instead of focusing on the detailed sequence of events leading up to the end of the relationship. The patient asks questions such as, "Why did my partner treat me like this? Why did I mess it up? Why can't I make relationships work? Why does this keep happening to me?"

TCPR: How do you explain rumination to a patient?

Dr. Watkins: I explain that it's a habit of overthinking and over-analyzing negative experiences. I'll also normalize it as something we all do. It's natural to think through problems until they make sense, especially when faced with losses, unresolved goals, or unexpected events. Indeed, in some situations rumination can be helpful—for example, thinking problems through can at times lead to useful problem solving.

TCPR: Can you further explain how rumination can also be beneficial for some people?

Dr. Watkins: Repetitive thinking about negative experiences can be productive and functional. It can lead to problem solving, learning, and coming to terms with upsetting experiences. However, rumination really refers to *unhelpful* negative thinking. So, to avoid confusion, I've introduced the idea of constructive versus unconstructive repetitive thought (Watkins ER, *Psychol Bull* 2008;134:163–206). But many ruminators do view their rumination as helpful. They see it as an attempt to understand, gain certainty, or problem solve after an upsetting experience. But that can be a double-edged sword: When patients view rumination as helpful, it can be harder to break out of the habit. Sometimes patients cannot differentiate between when they are brooding with rumination versus constructively solving a problem.

"RF-CBT focuses on changing the *process* of thoughts rather than challenging the *content* of negative thoughts. The goal is not to think about those problems less often, but to think about them in a more helpful way."

Edward Watkins, PhD

TCPR: Psychiatrists probably see a lot of ruminating patients. What are some ways they could guide patients to break that pattern in a brief therapy visit?

Dr. Watkins: Often this is something that hasn't been discussed with patients, but you can in a short session help them recognize that they are ruminating. The two key steps are first, to spot the warning signs for rumination, and second, to make a plan for an alternative, more helpful behavior in response to this trigger. Common warning signs for rumination are physical signs of anxiety (such as tension, feeling hot, or a sinking feeling in the stomach), attention narrowing, and self-doubt or self-criticism.

TCPR: What comes next?

Dr. Watkins: A simple and effective approach is to ask patients to write out an "if-then plan." For example, "If I notice that I am starting to get tense in my shoulders, then I will practice my relaxation exercises." The *if* part of the plan is the warning sign for rumination, and the *then* part is a constructive alternative. Writing out plans in this way helps patients remember to enact the new behavior when stressed. These plans—called implementation intentions—are proven to help with habit change. A wide range of behaviors can be useful alternatives, including relaxation, behavioral activation, explicit problem-solving, and compassion. It is best to choose a behavior that the patient can already do and has already found helpful at stopping rumination.

TCPR: What are some examples of a behavior we can choose?

Dr. Watkins: Activities that engage people directly in an experience, where patients are immersed in the moment, can be quite powerful. They are not evaluating what they are doing but are absorbed in it, and in this "absorbed" state, they are no longer ruminating. These activities vary greatly from individual to individual. For some, it involves engaging with nature. For others, it could be dance, socializing, exercise, or being creative: drawing, music, painting, cooking, or gardening.

TCPR: You've developed a therapy that helps patients here. Can you tell us more about rumination focused cognitive behavioral therapy (RF-CBT) and how it works?

Dr. Watkins: In RF-CBT, we view rumination as a habit. We help patients spot their triggers and identify more functional and adaptive behaviors to use in place of rumination. For example, a patient who ruminates with self-critical thoughts may perceive those thoughts as motivating—imagining that they keep the patient from making mistakes or from becoming lazy and complacent. In that case, the self-critical thoughts might be triggered by situations where the patient feels tired or is falling behind on a task. After identifying the triggers, we'd help the patient learn new behaviors that can serve the same purpose of self-motivation, such as self-compassion. Instead of harsh self-criticism, compassionate thoughts are a kinder way to coach yourself along. So,

Continued on page 4

Expert Interview
Continued from page 3

the therapy is built on a close functional analysis of the patterns of rumination and repeated practice of alternative behaviors (Watkins RW, *Rumination-Focused CBT for Depression*. New York, NY: The Guilford Press; 2018).

TCPR: So, you're helping patients change behaviors as well as thoughts, but how does RF-CBT differ from traditional CBT?

Dr. Watkins: RF-CBT focuses on changing the *process* of thoughts rather than challenging the *content* of negative thoughts. We seek to understand the whole sequence of thinking and then shift it. Key to this is understanding rumination as a common and normal attempt to address unresolved goals. When something goes wrong in our life, such as losing a job, it is natural to dwell on it, and attempts to stop those thoughts wouldn't work in the long run. The goal in RF-CBT is not to think about those problems less often, but to think about them in a more helpful way, and that has to do with the process of thoughts.

TCPR: Can you tell us more about what you mean by a focus on "the process of thoughts?"

Dr. Watkins: It's based on experimental work we've done, which suggests that the way that people think about negative experiences can determine whether that thinking is helpful or not (Watkins ER, *Psychol Bull* 2008;134:163–206). Specifically, abstract thinking tends to impair problem solving and prolong negative moods, whereas more concrete thinking tends to reduce negative moods and improve problem solving.

TCPR: What are some examples of the difference between abstract and concrete thinking?

Dr. Watkins: Abstract thinking focuses on the meanings, consequences, and implications of events, often in the form of "why" questions such as, "Why did this happen? Why can't I do this? Why am I still depressed?" Concrete thinking is more down to earth. It involves paying attention to what actually happens; the senses of what one sees, hears, and feels; the context; and the sequence of events. Concrete thinking involves more useful "how" questions, such as, "How did this happen? How can I do something about it?" This form of thinking can help people solve problems, move to effective action, learn from past situations, and keep difficulties in perspective.

TCPR: Can you give us a case example of this?

Dr. Watkins: Sure. Consider a mother with depression, who is struggling in her relationship with her teenage daughter. When we review her rumination over the last week, she reports a prolonged bout of rumination about an argument with her daughter. Her natural tendency is to think abstractly about the causes and meanings of this argument, with abstract questions such as, "Why doesn't she listen to me? Why am I a terrible mother?" This gets her stuck in prolonged self-criticism and self-blame. However, in the therapy session, we can help her focus on the same situation in a more concrete way and remember what led up to the argument, what exactly she said and did to her daughter, and what her daughter said and did in response, replaying it moment by moment as if in slow motion.

TCPR: Interesting. What happens next with the mother?

Dr. Watkins: By focusing on those concrete details, she can recognize points where she could have done something differently to prevent the argument from escalating—for example, stepping away from the conflict for a few minutes to calm down and problem-solve.

TCPR: Does this approach also help patients come to terms with past upsetting events?

Dr. Watkins: Yes. For example, another patient may be spending a lot of time ruminating about a painful divorce. When we look at this more closely in therapy, the trigger for her rumination about the divorce is whenever an intrusive memory of difficult encounters with her ex-husband pops into her mind. However, rather than spending time with these memories and habituating to them, the patient starts asking, "Why did this happen?" and dwelling on what the failure of the marriage says about her. This temporarily takes the patient away from staying with these upsetting memories, but it also tends to lead to self-blame and negativity. In RF-CBT, we'd encourage her to stay with the details of those memories: the sensory details and the concrete specifics. That would help her process what happened, stop blaming herself, and work through her sadness and anger about the end of the relationship.

TCPR: Is rumination unique to depression, or does it cross diagnostic boundaries?

Watkins: There is good evidence that rumination is transdiagnostic and plays a causal role in a range of different disorders, including depression, anxiety, eating disorders, psychosis, and substance use disorders (Nolen-Hoeksema S & Watkins ER, *Perspect Psychol Sci* 2011;6(6):589–609). It appears to be a final common pathway between stressful experiences and pathology (Watkins ER & Nolen-Hoeksema S, *J Abnorm Psychol* 2014;123(1):24–34). For example, consider a patient who experienced major stress in early childhood. That patient might try to make sense of the childhood events by thinking about them repeatedly, and that rumination drives further stress and symptoms.

TCPR: Have the brain circuits involved in rumination been identified?

Dr. Watkins: There is extensive study of the brain circuits linked to rumination, and a growing pattern of evidence points to increased activation of the default mode network. That network is involved in the thoughts people have when they are not focused on a particular task. Reduced inhibition from the cognitive control network has also been linked to rumination (Jacobs RH et al, *PLoS One* 2016;11(11):e0163952). Moreover, we have some preliminary evidence that RF-CBT can change these patterns of brain activation.

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

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Antidepressant Augmentation Strategies: A Basic Guide

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

Here's a common scenario. You have a patient who has tried three or four antidepressants over the years; all have been somewhat effective at least initially, but eventually that effectiveness waned.

Let's imagine that the patient you're seeing now is on antidepressant number 4, Lexapro, at a solid 20 mg dose. You could always keep pushing the dose, but there's little evidence for this. You could switch to yet another antidepressant, but your intuition says it's time to augment. Plus, recent studies have reported that augmentation outperformed placebo by 2:1 (Zhou X et al, *J Clin Psych* 2015;76:e487–e498), and that switching medications was no more effective than doing nothing (Bschor T et al, *J Clin Psych* 2018;79).

Drawing from both the literature and my own clinical experience, the following is a reasonable approach to choosing an augmentation strategy.

Atypical antipsychotics

The atypicals are the best-studied TRD augmentation agents, and among atypicals I favor aripiprazole for a couple of reasons: It has more positive trials than the other atypicals, and along with the less-well-studied risperidone, aripiprazole was one of only 2 atypicals that improved functioning and quality of life in a recent meta-analysis (Zhou X et al, *Int J Neuropsychoph* 2015;18:pyv060).

To avoid the most common side effect of akathisia, start low and increase slowly (eg, start with 1–2 mg daily for 7 days then 5 mg daily). Have patients start by taking it in the morning—although tell them that because it causes fatigue in about 10% of patients, they might prefer evening dosing. The 2 mg dose is no better than placebo, and aripiprazole has dose-dependent benefits (and side effects) between 5–15 mg per day. The average dose in the efficacy trials was 11 mg, but I usually allow an adequate trial at 5 mg (2–4 weeks) before raising the dose.

After aripiprazole, my choice is usually guided by side effects and costs, but the path around those side effects is rarely clear of thorns. Those with less sedation and weight gain (aripiprazole, brexpiprazole, cariprazine) tend to cause more akathisia. In the depression trials, overall tolerability was highest for risperidone and lowest for quetiapine. However, quetiapine's low rate of akathisia and EPS makes it attractive for some patients, and risperidone's high rate of prolactinemia is a drawback for others. Ziprasidone has the lowest risk of weight gain and metabolic effects, but the data supporting its use in augmentation are limited to a single positive trial, and ziprasidone carries additional risks of QT prolongation.

Generally, the atypicals can work with any antidepressant, although most were paired with an SSRI in the augmentation trials. One exception is olanzapine, which is FDA-approved only as an augmenter to fluoxetine in the form of OFC. Eli Lilly, which patented olanzapine and fluoxetine, sought approval for its combined OFC product in TRD rather than studying its antipsychotic for more general augmentation. That story takes an ironic turn in Zhou's meta-analysis of atypicals in TRD, where OFC turned out to have the lowest efficacy despite being the only medication with a specific TRD indication. Zhou's study turned up a different kind of surprise for the off-label risperidone, whose efficacy for antidepressant augmentation surpassed that of 2 FDA-approved options (quetiapine and OFC).

Augmentation Strategies for Treatment-Resistant Depression

Medication	Dose
Best evidence: Positive results in controlled trials and network meta-analyses	
Aripiprazole*	5–15 mg/day
Quetiapine*	150–300 mg/night
Risperidone	0.5–3 mg/night
Lithium*	Serum level 0.5–0.8 mmol/L
Triiodothyronine	50 mcg/day
Moderate evidence: Mixed results in controlled trials and network meta-analyses	
Olanzapine*	5–15 mg/day with fluoxetine
Tricyclics*	Nortriptyline has the best evidence (start 25–50 mg/day, raise weekly toward serum level of 50–150 ng/mL)
Buspirone	15 mg TID (start 5 mg BID)
Promising: Positive results in 1–2 controlled trials	
Brexpiprazole*	3 mg/day
Cariprazine	1.5–4.5 mg/day
Ziprasidone	20–80 mg BID with a full meal
Mirtazapine*	15–45 mg/night
Pramipexole	1–2 mg/night (start 0.25 mg and titrate every 5–7 days)
D-cycloserine	1,000 mg/day (glutamatergic antagonist)
L-methylfolate*	15 mg/day
SAMe	400–1,600 mg/day
Unlikely to work: Controlled trials are largely negative	
Pindolol, bupropion, lamotrigine, methylphenidate, lisdexamfetamine, modafinil	

* FDA-approved options for depression are starred

The efficacy of these agents is flipped in bipolar depression, where the effect size is largest for OFC and almost negligible for aripiprazole (Taylor DM et al, *Acta Psychiatr Scand* 2014;130:452–469). In bipolar depression, the atypicals should be used as monotherapy, except for olanzapine, which only works when combined with fluoxetine. In contrast, all of these agents require an antidepressant to work in unipolar depression, unless mixed features are part of the presentation, in which case they may work on their own—lurasidone has the best evidence for those cases (Suppes T et al, *Am J Psychiatry* 2016;173(4):400–407).

Lithium

After the atypicals, lithium is the second-best studied augmentation option for TRD, but I would consider it first-line in patients who are at risk for suicide. Lithium's antisuicide effects are supported by epidemiologic data as well as controlled studies, and they are partly independent of its effects on mood. In a meta-analysis of 34 studies involving 110,000 person-years, lithium reduced the risk of suicide fivefold in recurrent unipolar depression and sixfold in bipolar disorder (Tondo L et al, *Curr Psychiatry Rep* 2016;18:88). A more recent case-control study has confirmed that effect and added another 410,000 life-years to the data (Song J et al, *Am J Psychiatry* 2017;174(8):795–802).

Lithium's tolerability is comparable to the atypicals, and its side effects are further reduced by starting low (150–300 mg) and raising slowly (every 5 days toward 900 mg). From that point, I'll dose by serum level (0.5–0.8 mmol/L is ideal for depression). Response should be seen in 2–6 weeks of achieving

Continued on page 6

Antidepressant Augmentation Strategies: A Basic Guide

Continued from page 5

an adequate level. The controlled release versions reduce most side effects by about 50%, although they can cause more diarrhea.

Lithium's main drawback is the risk of renal insufficiency, which is reduced by giving the entire dose at night (Gitlin M, *Int J Bipolar Disord* 2016;4:27). Check labs (basic chemistries, calcium, TSH, and lithium level) every 6–12 months and consult a nephrologist if the creatinine rises above 1.5. Hypothyroidism is relatively common on lithium (10%–20%), and even subclinical hypothyroidism may be worth treating. In a controlled trial of bipolar depression, lithium worked best when the TSH was maintained around 2.4 mIU/mL (Frye MA et al, *Acta Psychiatr Scand* 2009;120:10–13).

Thyroid

Augmenting an antidepressant with thyroid is often overlooked but well-supported by the data. Thyroid, lithium, and the atypicals were the only augmentation agents that reached statistical significance for TRD in Zhou's meta-analysis of 48 studies. All those options carry medical risks, and in the case of thyroid, the concerns are arrhythmia, bone demineralization, and hypoglycemia (in diabetics). Thyroid augmentation is more effective in patients with subclinical hypothyroidism, but those with normal TSH levels can benefit as well.

Among the thyroid formulations, T3 (liothyronine, or Cytomel) is better studied than T4 (levothyroxine, or Synthroid) and was superior to T4 in a double-blind comparison (Joffe RT et al, *Neuroendocrin Letters* 1987;9:172). T3 is the more active form in the central nervous system, and some patients have difficulty converting T4 to T3. After checking a baseline thyroid panel, I will start T3 at 12.5–25 mcg/day and increase every 7 days toward a dose of 50 mcg daily. A thyroid panel should be checked at baseline and 4–6 weeks after reaching the target dose. Routine TSH can be checked every 6 months, and the dose should be lowered or discontinued if TSH < 0.5 mIU/L.

Other augmenters

Mirtazapine can reduce common serotonin side effects such as nausea, insomnia, akathisia, and sexual dysfunction, thus it is useful for augmenting serotonergic medications. Its use is backed by small studies, and a large trial is underway. L-methylfolate works preferentially in patients who are older, obese, or carry the MTHFR c-677t allele (Papakostas GI et al, *J Clin Psych* 2014;75:855–863).

I've tried many other emerging treatments, from statins to celecoxib, and the one I've seen the most benefit with is pramipexole. This dopaminergic agent treats both unipolar and bipolar depression with a large effect size, so it is a good choice when the diagnosis is unclear. In a small, controlled trial of TRD, it had a modest effect, and open-label data suggest it may work in cases that are resistant to ECT (Cusin C et al, *J Clin Psychiatry* 2013;74(7):e636–641). Outside of nausea, pramipexole is well-tolerated, with negligible effects on weight, sex drive, and cognition. The main concern with its use is pathological gambling, which can also occur with other dopamine agonists, such as aripiprazole. The gambling does not present with manic symptoms and is instead part of a spectrum of compulsive-hedonic behaviors that can happen with dopaminergics, such as shopping, masturbation, or excessively organizing the garage (Aiken C, *J Clin Psych* 2007;68:1230–1236).

Despite failing in research, a few augmentation strategies remain common in practice, including bupropion and the stimulants (specifically methylphenidate and lisdexamfetamine). I would use these as a last resort—I tend to take heed when manufacturer-supported trials are unable to show a benefit for their product, as was the case with these (including a large bupropion study that is unpublished). Novel stimulants (modafinil and armodafinil) have a limited role in treating apathy and fatigue, but patients usually appreciate that relief (Zhou X et al, *J Clin Psych* 2015;76:e487–e498).

When to stop?

I'll attempt to slowly withdraw an augmentation agent after 3–6 months of recovery, especially if it poses medical risks. The slower the taper, the better: at least 3 months for lithium and 2–6 weeks for others.

Switching and raising the dose

Switching antidepressants is the least effective strategy in TRD but may work after 1 failed trial. Evidence supports a small benefit with switches to venlafaxine, vortioxetine, the tricyclics (especially in melancholic depression), and the MAOIs (especially in atypical depression) (Cowen PJ, *Psychol Med* 2017;47:2569–2577).

Raising the dose is a common strategy, especially for an antidepressant that's become less effective over time, but controlled trials support a dose-dependent response for only a few antidepressants: MAOIs, tricyclics, bupropion, venlafaxine, mirtazapine, and vortioxetine (but not vilazodone).

What about ECT and TMS? These are beyond the scope of this article but should never be far from consideration in TRD. ECT remains the gold standard, with efficacy that surpasses that of TMS or any medication strategy (Berlim MT et al, *Depress Anxiet* 2013;30:614–623).

Seven Lifestyle Interventions for Treatment-Resistant Depression

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

Treatment-resistant depression (TRD) is not untreatable. The challenge is to keep hope alive and the patient engaged in recovery. "You deserve, and can expect, a full recovery," I'll often tell patients, "but we're going to need more than medications to get you there." I'll then offer a choice: to either start weekly psychotherapy or make a lifestyle change—or both.

Lifestyle factors influence the actions of antidepressants down to the cellular level. Animal and human studies consistently find that aerobic exercise, social interaction, and a stimulating environment enhance both the clinical and biological effects of antidepressants, such as by increasing neurotrophic factors and synaptic plasticity. In some studies, antidepressants have failed to work unless the right environmental factors were in place (Rief W et al, *Neurosci Biobehav Rev* 2016;60:51–64).

That model of depression can help engage patients who have been lulled into passivity as they wait for the right medication to change their brain chemistry. After describing the rationale, I'll offer patients a menu of options and advise them to select only one. I'll say, "Your motivation is limited, so let's invest it in something we know can make your medications work better."

The following are lifestyle changes I recommend to my TRD patients. More details, including patient-ready brochures, are at moodtreatmentcenter.com/lifestyle.

Brisk walking

I tell patients, "I don't want you to exercise—that's too difficult. Just start walking briskly." Fortunately, the type of exercise with the best evidence in depression is relatively mild: less than a jog but more than a walk. The ideal dose is 30 minutes a day or 45 minutes every other day. It works as well as an antidepressant, augments antidepressants, and improves treatment-resistant depression (Mura G, *CNS Spectr* 2014;19:496–508). I'll often start by prescribing a lighter dose, such as 10 minutes a day. Patients who prefer the indoors have found sites such as WalkAtHome.com helpful.

A slow forest walk

If a brisk walk is too intimidating, a stroll in the woods may provide similar relief. In one study, a 90-minute forest walk reduced ruminative thinking more than a similar urban walk. It also lowered neural activity in an area of the brain involved in behavioral avoidance: the subgenual prefrontal cortex (Bratman GN et al, *Proc Natl Acad Sci* 2015;112(28):8567–8572). Additionally, walking in the woods improves cognitive performance better than a walk in the city or suburbs. Other natural environments, such as gardens and bodies of water, have similar effects.

Regular wake times

Cognitive behavioral therapy for insomnia (CBT-i) is a first-line treatment for insomnia, and about a dozen clinical studies have found it effective for depression as well (Cunningham JE et al, *J Psychosom Res* 2018;106:1–12). Online CBT-i can also work (myshuti.com has passed in a clinical trial) and there's a free app-guided version sponsored by the VA (mobile.va.gov/app/cbt-i-coach). If patients are unable to take on the full therapy, I'll advise them to stick to the most important behavioral piece: rising out of bed at the same time each morning.

Dawn simulator

Ask depressed patients how long it takes them to feel fully awake, and they may answer in terms of hours rather than minutes. That's due to a little-known symptom of depression called *sleep inertia*, and it improves with a dawn simulator. These devices create a virtual sunrise in the bedroom, and they worked for winter depression in 6 small, controlled trials (Danilenko KV et al, *J Affect Disord* 2015;180:87–89). They are slightly less effective than a lightbox but much easier to use, and they can help patients stick to a regular wake time.

Mediterranean diet

In 2017, following 2 controlled trials from Australia (Parletta N et al, *Nutr Neurosci* 2017:1–14), we saw the first clinical evidence that dietary change can improve depression. Based on the Mediterranean diet, which can enhance neuroplasticity and reduce inflammation, the intervention improved depression with a large effect size (see "An Antidepressant Diet," *TCPR* April 2018).

Mindfulness or breathing meditation

Along with brisk walking, these interventions work not only in depression, but in treatment-resistant populations as well (Sharma A et al, *J Clin Psych* 2017;78:e59–e63). Granted, they are more likely to work if they are undertaken with a therapist or instructor, but patients who are unable to do that may find some benefit through regular independent practice. Guided mindfulness is available through CDs, music streaming services, and apps. An expert review of mindfulness apps gave high marks to Headspace, Smiling Mind, iMindfulness, and Mindfulness Daily (Mani M et al, *JMIR Mhealth Uhealth* 2015;3:e82).

For breathing meditation, the forms with the best evidence are rhythmic breathing and Sudarshan Kriya yoga. Among apps, Breathe2Relax is a useful tool.

Antidepressant apps

I have been skeptical of therapy by smartphone, but there is more and more evidence that it can make a difference even in the absence of a therapist (see "A CBT App for Refractory Depression," page 10). For the motivated patient who can't afford therapy, apps are a helpful coach, guiding changes of a more complex nature than the ones I've listed above. Among apps with a CBT focus, the following have some research support: Moodivate, Happify, Stress Free, Virtual Hope Box, and Intellicare (Rathbone AL et al, *J Med Internet Res* 2017;19:e399).

A Primer on MAOIs

Monoamine oxidase inhibitors (MAOIs) may be particularly beneficial for our patients with atypical depression, social anxiety disorder, and treatment-resistant depression (TRD). Yet, a lack of familiarity with the drugs and propagation of outdated dietary restrictions have caused many of us to shy away from prescribing MAOIs.

The decline in MAOI use has been well-documented. In a 1997 survey, one-third of psychiatrists reported they had not prescribed an MAOI in the past few years, and their use has declined by at least 50% in the years since (Shulman KI et al, *J Clin Psychiatry* 2009;70(12):1681–1686; Balon R et al, *Psychiatr Serv* 1999; 50(7):945–947).

Getting to know MAOIs again

Our first step? Review their basic pharmacology. The monoamine oxidase (MAO) enzyme has two subtypes, MAO-A and MAO-B, and they metabolize different neurotransmitters. The MAO-A enzyme metabolizes norepinephrine, epinephrine, serotonin, and dopamine. Meanwhile, MAO-B metabolizes dopamine and tyramine (a vasoactive amine).

The older MAOIs, tranylcypromine, phenelzine, and isocarboxazid, cause irreversible inhibition of both MAO-A and MAO-B. That means they increase norepinephrine, serotonin, and dopamine. The dopaminergic effects are strongest for tranylcypromine.

Selegiline transdermal (Emsam), the newest MAOI on the market, is also irreversible, but it has a slightly different pharmacology. At low doses (6 mg/day), it is selective for MAO-B, but it becomes unselective at the higher doses often needed for depression (9 mg/day–12 mg/day). Theoretically, the transdermal absorption of the drug should minimize the effect on tyramine in the gut, but MAOI dietary restrictions are still recommended at any dose over 6 mg/day.

For completeness, we should mention one other agent: moclobemide is a reversible, MAO-A selective MAOI. It isn't available in the US, but it is approved in Canada. Because it is specific to MAO-A, there are no dietary interactions, but it also does not appear to be as effective as the irreversible, non-selective MAOIs for depression.

How effective are MAOIs?

Many studies have compared MAOIs with tricyclic antidepressants (TCAs). A meta-analysis published in 2006 concluded that older MAOIs might be more effective than TCAs for atypical depression (Henkel V et al, *Psychiatry Research* 2006;141:89–101). In another study of 47 patients whose depression had failed to respond to at least 2 TCAs, 50% had a response to tranylcypromine (Nolen WA et al, *Acta Psychiatr Scand* 1988;78(6):676–683). Multiple studies have also found MAOIs to be effective for social anxiety and dysthymic disorder, and pilot data suggests benefits in panic disorder, posttraumatic stress disorder, and bulimia.

The newest MAOI, transdermal selegiline, was approved by the FDA in 2006 for major depressive disorder. The transdermal form has not been studied in atypical and treatment-resistant populations, but oral selegiline has at doses between 20 mg–60 mg/day (20 mg of oral selegiline equates to 6 mg/day of transdermal). Oral selegiline, however, carries a higher risk of food and drug interactions.

Adverse effects; food and drug interactions

Adverse effects

Adverse effects are often cited as a reason to avoid MAOIs. However, the adverse effect profiles of the older MAOIs tend to be similar in severity and frequency to those of the selective serotonin reuptake inhibitors (SSRIs). Although they cause more hypotension than SSRIs, MAOIs are less likely to cause gastrointestinal problems. All 3 older MAOIs can cause a moderate amount of agitation, insomnia, weight gain, and sexual dysfunction.

What about the selegiline patch? Compared with SSRIs and older MAOIs, this agent has a more attractive side effect profile, with minimal weight gain, fatigue, and sexual dysfunction. The most common adverse reaction is skin irritation, which can be managed by rotating the application site or using hydrocortisone cream (allow it to dry before applying the patch).

Food interactions

Food interactions are another common reason that physicians avoid MAOIs. Unfortunately, most of the published material on dietary restrictions derives from an era where tyramine concentrations

Continued on page 9

Available MAOIs for Depression in the US

Drug (Brand Name)	Starting Dose/Usual Therapeutic Dose	Common Adverse Effects	Approximate Price per Month[1]
Tranylcypromine (Parnate)	• Starting: 10 mg once or twice daily • Usual: 30 mg–60 mg/day	Sexual dysfunction, orthostatic hypotension, insomnia, agitation, peripheral edema	$90[2]
Isocarboxazid (Marplan)	• Starting: 10 mg once or twice daily • Usual: 30 mg–60 mg/day	Sexual dysfunction, orthostatic hypotension, weight gain, insomnia, sedation, peripheral edema, vitamin B_6 deficiency	$420[3]
Phenelzine (Nardil)	• Starting: 15 mg once or twice daily • Usual: 45 mg–90 mg/day	Sexual dysfunction, weight gain, orthostatic hypotension, insomnia, sedation, peripheral edema, vitamin B_6 deficiency	$30[2]
Selegiline transdermal (Emsam)	• Starting: 6 mg/day patch • Usual: 6 mg–12 mg/day patch	Insomnia, topical reactions at patch site, false positive on drug screen	$1,700[3]

[1] At lowest maintenance dose—pricing information from Rxpricequotes.com

[2] Two manufacturers—generic and brand available

[3] Only available as a branded product from one manufacturer

A Primer on MAOIs

Continued from page 8

could not be accurately measured in food. Since 2000, improvements in technology have clarified which foods truly contain a concerning amount of tyramine and which foods are perfectly safe in normal serving sizes. For further details about food interactions with MAOIs, an extensive review of current literature is available online at https://psychotropical.info/wp-content/uploads/2017/12/MAOI_diet_drug_interactions_2016.pdf.

Drug interactions

MAOIs have two dangerous drug interactions: hypertensive crisis and serotonin syndrome. Drugs that cause these include over-the-counter agents (L-tryptophan, St. John's wort, and decongestants containing phenylephrine, pseudoephedrine, or dextromethorphan), prescription medications (antidepressants, buspirone, psychostimulants, fenfluramine, meperidine, and possibly carbamazepine and cyclobenzaprine), and drugs of abuse (cocaine, amphetamines, MDMA, and excessive alcohol). Due to the potential for interactions with pain and anesthetic agents, surgery requires caution. Ziprasidone is the lone antipsychotic that cannot be combined with an MAOI.

Dietary Guidelines for MAOIs

Foods to Avoid Completely	• Highly aged, artisanal cheese • Homemade or artisanal sourdough bread • Any fermented soy bean products (most often found in Asian foods)[1] • Raw meat or fish that has not been refrigerated properly or is past the "use by" date • Aged beef (usually only found at high-end restaurants) • Homemade beer or wine • Any highly aged or fermented product until tyramine content can be verified
Acceptable in Small Portions (smaller than a typical serving size)	• Specialty soy sauce • Dried, aged sausage (usually from Europe) • Sauerkraut • Low-volume/micro-brewed beer made using natural yeast/spontaneous fermentation—limit to 1 drink consumed with food (avoid on an empty stomach)
Acceptable in Normal Portions (typical serving size—but could be problematic if consumed in excess)	• All other types of cheese (except those listed above and below) • Fermented yeast products (Marmite and Vegemite) • Kimchi • Commercial soy sauce (grocery store brands) • Worcestershire sauce • Fish sauce • Sourdough bread (commercial production) • Fresh beef or fish—if properly refrigerated and eaten by the "use by" date • Bananas (except the peel) and avocados—but avoid if they have gone bad or are past the "use by" date • Chocolate • Caffeine-containing beverages (coffee, tea)[2] • Wine from a commercial producer, red or white (serving size 2 glasses) • Beer from a commercial producer (pasteurized) (serving size 2 pints)
No Restrictions (no significant tyramine content)	• Milk, yogurt, cream • Non-matured, soft cheese (eg, ricotta, mozzarella, cottage cheese, cream cheese) • Dry, cured meats (eg, prosciutto, parma ham) • Smoked or pickled fish (if properly stored) • Fresh chicken, duck, pork, and sausage (if properly stored) • Stock cubes, powder, or bullion for making soup • Non-fermented soy bean products

[1] This only applies to *fermented* soy bean products—see https://en.wikipedia.org/wiki/List_of_fermented_soy_products

[2] Does not contain tyramine, but sensitivity to caffeine can increase when taking MAOIs, so moderation is recommended

Table created using information from https://psychotropical.info/wp-content/uploads/2018/02/3_MAOI_Diet_Abbreviated_2016_3.1-1.pdf

To prevent serotonin syndrome, a washout period is required between stopping an antidepressant and replacing it with an MAOI. Generally, the old drug should be tapered down over 1–2 weeks (fluoxetine and vortioxetine can be stopped abruptly because of their long half-lives). Once the old drug is completely stopped, you should allow for a washout period equivalent to 5 half-lives of the old drug before starting the MAOI. Benzodiazepines can be used to relieve any distress that arises during that drug-free period.

Starting a patient on an MAOI

Who is a candidate for an MAOI?

Patients who have failed several trials of other agents for major depression, as well as those with atypical depression, panic disorder, or social anxiety disorder, are candidates for MAOIs.

Key points for patient education

1. Teach about the important drug interactions
2. Educate about food interactions (including information about outdated dietary advice)
3. Stress the importance of notifying other healthcare professionals about the drug (doctors, pharmacists, dentists, etc)

Which is the best MAOI to start with?

Tranylcypromine and phenelzine are often considered the first-line choices in the MAOI class, but opinions vary, and we lack extensive head-to-head comparison data. Phenelzine is the best-studied MAOI for atypical depression and is currently the most affordable MAOI. Other experts recommend tranylcypromine, which is less likely to cause weight gain or sedation than the other 2 classic MAOIs.

Transdermal selegiline may have a different niche. Although its favorable side effect profile makes it an attractive option, it lacks research in the types of depression that typically draw us toward MAOIs: atypical and TRD.

Dosing

Start at the lowest dose and titrate slowly (every 3–7 days). But remember that MAOIs have a dose-dependent response,

Continued on page 10

Research Updates IN PSYCHIATRY

DEPRESSION

A CBT App for Refractory Depression

REVIEW OF: Mantani A et al, *J Medical Internet Res* 2017;19(11):e373

Mobile phones have allowed the introduction of guided, self-help cognitive behavioral therapy (CBT) for depression with enhanced accessibility, efficiency, and affordability. Several meta-analyses suggest that computers can augment face-to-face psychotherapy and even work on their own through self-guided programs. Most of those studies involved patients with mild to moderate depression, which leaves open the question of how well this approach would work in more severe cases.

This study tested a self-guided mobile app in patients with moderate to severe depression who had not responded to at least 1 antidepressant trial. The Japanese app, called Kokoro, used cartoon characters to present concepts from CBT, including self-monitoring, behavioral activation, and cognitive restructuring.

The authors randomized 164 patients to an intervention group (medication switch plus Kokoro app) and control group (medication switch only). Although the treatments were not blinded, the outcomes were assessed with blinded raters.

After 9 weeks, the intervention group showed greater improvement in the Patient Health Questionnaire-9, the primary outcome measure ($p < 0.001$). Rates of remission (18% vs 10%) and response (32% vs 18%) were also greater, and the magnitude of the benefit compared favorably with the effect sizes seen in antidepressant trials.

In the second phase of the study, both groups were given access to the app for an additional 2 months. After that time, both groups had similar depression scores. The intervention group maintained their gains, and the control group caught up.

Most patients stayed engaged with the 8-session app, but that engagement was not entirely self-driven. Each week, participants received a brief, personalized email congratulating them on their progress.

TCPR'S TAKE

This study demonstrates significant benefits for this CBT app in difficult-to-treat depression. Its strengths include a randomized controlled design, blinded ratings, and high levels of engagement and completion. The main limitation is the lack of blinding in the treatment arm, which makes it difficult to rule out a placebo effect. By making changes to medications in both groups at the start of the trial, the authors attempted to minimize expectancy effects.

For clinicians, the main limitation may be the inaccessibility of the Japanese-language app, a common problem in this type of research. Most of the available mental health apps are untested, and most of the tested apps are not available. A reasonable substitute is Intellicare, a suite of CBT-based apps made free through NIMH funding. These apps looked promising in an uncontrolled study, and a large, randomized controlled trial of Intellicare is nearing completion (intellicare.cbits.northwestern.edu).

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

A Primer on MAOIs

Continued from page 9

so if the patient has not achieved an adequate response to initial therapy, a higher dose might help.

Managing side effects

Orthostasis can be a problematic side effect. Remedies include dose reduction, increasing fluid intake (8 glasses of water a day), support stockings, and lowering concurrent antihypertensives. In severe cases, fludrocortisone can be used (0.5 mg 1–2 PO Q6hr PRN).

Insomnia may improve by shifting the dose to morning or using a hypnotic (all the FDA-approved options are safe with MAOIs except for doxepin/Silenor).

Discontinuation

Rarely, abrupt discontinuation of an MAOI triggers psychotic delirium, so they should be tapered slowly over 2 weeks. Wait another 2 weeks after discontinuation before lifting the dietary and drug restrictions or starting a new antidepressant (including another MAOI).

What about augmentation?

Therapy with MAOIs can be augmented with several drugs. Lithium has the most evidence, and second-generation antipsychotics (except ziprasidone) can also be used. Augmentation with other psychotropics is more controversial, but a literature review suggests it may be feasible with careful monitoring. The evidence is sparse, but the best studied options are the psychostimulants, trazodone (for insomnia), and certain tricyclics (especially trimipramine). Highly serotonergic medications (eg, SSRIs, SNRIs, clomipramine) should be avoided completely (Thomas SJ et al, *Pharmacotherapy* 2015;35(4):433–449).

TCPR'S TAKE

When patients have not recovered fully on an antidepressant, MAOIs are worth considering. In atypical depression, MAOIs hold the unique distinction of being more effective than another class of ADs. They should always be part of the conversation in treatment-resistant depression and treatment-resistant anxiety disorders.

MAOIs are much simpler to use than their reputation suggests. They are reasonably well-tolerated, and their drug interactions and dietary restrictions are not overly burdensome for most of the patients who take them.

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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 are listed on page 1.

1. What percentage of patients with treatment-resistant depression are diagnosed with bipolar disorder after structured testing? (LO #1)

   [ ] a. 0.5%–4% [ ] b. 5%–15% [ ] c. 20%–35% [ ] d. 40%–60%

2. According to Dr. Watkins, people who ruminate are more likely to: (LO #2)

   [ ] a. Act on suicidal thoughts
   [ ] b. Benefit from pharmacologic vs therapeutic treatments
   [ ] c. Experience further episodes of depression in the future
   [ ] d. Benefit from a combination of medication and dialectical behavior therapy

3. According to Dr. Aiken, switching antidepressants is usually more effective than augmentation for patients with treatment-resistant depression. (LO #1)

   [ ] a. True [ ] b. False

4. According to Dr. Watkins, rumination focused cognitive behavioral therapy (RF-CBT) views rumination as which of the following? (LO #2)

   [ ] a. A disorder [ ] c. A cognitive distortion
   [ ] b. A habit [ ] d. A phobic response

5. According to a recent study, patients with moderate to severe depression who used a self-guided CBT-based mobile app experienced improvements in depression, but the rates of remission and response were much lower than those seen in antidepressant trials. (LO #3)

   [ ] a. True [ ] b. False

6. According to Dr. Aiken, which of the following medications is the most appropriate first-line choice for antidepressant augmentation in a patient with treatment-resistant depression who is also suicidal? (LO #1)

   [ ] a. Gabapentin [ ] b. Mirtazapine [ ] c. Lithium [ ] d. Valproate

7. According to Dr. Aiken, using rating scales, such as the Patient Health Questionnaire-9 (PHQ-9), can contribute to improved outcomes in patients who have treatment-resistant depression. (LO #1)

   [ ] a. True [ ] b. False

8. What was the main limitation in a recent study testing a CBT-based mobile app for patients with moderate to severe depression? (LO #3)

   [ ] a. High dropout rates
   [ ] b. Outcomes assessed with non-blinded raters
   [ ] c. Low levels of engagement with the app
   [ ] d. Lack of blinding in the treatment arm

THE CARLAT REPORT: PSYCHIATRY

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This Month's Focus:
Treatment-Resistant Depression

Next month in *The Carlat Psychiatry Report:*
Emergency Psychiatry

Treatment-Resistant Depression: Some Introductory Tips

Continued from page 2

with or without routine measurement, remission rates were more than double among those who rated their depression at each visit (29% vs 74%). Both groups were restricted to the same medications (paroxetine and mirtazapine), but the measurement-based group followed an algorithm to adjust the doses based on the self-rated Quick Inventory of Depressive Symptomatology (QIDS) scale (http://media.mycme.com/documents/13/mdd-qids_3069.pdf), while the control group based their treatment changes on the physician's impression (Guo T et al, *Am J Psych* 2015;172:1004–1013).

I use the Patient Health Questionnaire-9 (https://tinyurl.com/ydfvfso5) at every visit and have found that graphing the results can reveal long-term patterns I otherwise would have missed. Often a patient will convince me that a new medicine has "done nothing," until I peek at the patient's ratings and see that they demonstrate a slow but steady improvement. In the past I would have stopped that medicine, or the patient may have elected to stop it. Now I show the data to the patient, and we decide together whether things are moving in the right direction.

Never give up

Hopelessness is contagious. I keep a long list of options for TRD on my desk to ensure I don't fall into the counter-transference trap of giving up and doing nothing. I've also learned not to cross past medications off that list, even when patients convince me of their futility. Depression, after all, can cloud the recall of past success.