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Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Practical Psychotherapy

Learning Objectives

After reading these articles, you should be able to:

1. Evaluate the benefits of ramelteon for insomnia.
2. Identify the advantages and disadvantages of specific SSRIs.
3. Describe best practices for psychotherapy to reduce side effects.
4. Summarize some of the current research findings on psychiatric treatment.

Is Ramelteon an Effective Hypnotic?

Randall Moore, MD, JD. Clinical Associate Professor, Department of Psychiatry and Behavioral Sciences at Texas A&M Health Science Center College of Medicine. Chris Aiken, MD. Editor-in-Chief of TCPR. *Practicing psychiatrist, Winston-Salem, NC.*

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

Ramelteon (Rozerem) stands out from other hypnotics in several ways:

1. It is not a controlled substance and has no risk of addiction or withdrawal.
2. It is relatively safe in the elderly.
3. It has a low risk of falls and complex sleep behaviors.

However, ramelteon's use has been limited by its high cost and modest efficacy. Now that it's gone generic, we'll

Highlights From This Issue

All effective treatments have side effects, argues Dr. Linden. Psychotherapy side effects are not the result of bad therapy; they are simply unwanted effects of a therapy that's correctly applied.

Transcranial direct current stimulation (tDCS) has antidepressant effects, according to a new meta-analysis.

Benzodiazepines and SSRIs may interfere with learning in psychotherapy, and Dr. Sudak shows us how to work around that.

There's no such thing as "the best" SSRI, but your patient's age, drug interactions, and psychiatric diagnosis can help personalize the selection.

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Q&A With the Expert

Side Effects of Psychotherapy
Michael Linden, MD, PhD

Professor of psychiatry and director of psychosomatic research at the Charité University Medicine Berlin, Germany. Dr. Linden has dual training as a psychologist and psychiatrist and is licensed as a cognitive behavior therapist. He has helped develop new branches of CBT, and his research has brought recognition to the potential side effects of psychotherapy.

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

TCPR: What are side effects to psychotherapy?
Dr. Linden: Side effects are adverse reactions to a therapy that is correctly applied.
TCPR: Why do you say "correctly" applied?
Dr. Linden: When I talk about side effects, I'm not talking about boundary violations or mistakes by the therapist. I'm talking about unwanted events that are caused by the treatment. Side effects are common negative effects that occur in all psychotherapies just as they do with most medical therapies. Now, there are many unwanted events that can happen over a course of psychotherapy, and it can be challenging to figure out which ones are caused by the therapy. The patient may get divorced or get into conflicts at work. New symptoms may emerge, or they may not respond to the treatment.
TCPR: Can you give an example of side effects?

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Is Ramelteon an Effective Hypnotic?

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look back on its 15-year tenure to figure out where this novel hypnotic stands.

How it works

Ramelteon is a synthetic analog of melatonin. It is an agonist at the melatonin receptors that regulate sleep and circadian rhythms and binds to them with greater affinity than natural melatonin. Those receptors are MT_1 and MT_2. MT_1 promotes sleep by inhibiting wakefulness signals from the suprachiasmatic nucleus. MT_2 synchronizes the circadian clock that regulates the 24-hour sleep cycle.

Tasimelteon (Hetlioz) has similar properties to ramelteon but is only FDA approved for insomnia in people whose circadian clocks are out of sync because of blindness.

A small but real effect

Compared to placebo, ramelteon helps patients with primary insomnia fall asleep 4–9 minutes faster (Kuriyama A et al, *Sleep Med* 2014;15(4):385–392). That might sound fairly unimpressive, but it's only a few minutes behind the other hypnotics (see table). It appears to work about as well as melatonin (0.5–5 mg qhs), but ramelteon has never gone head-to-head with another hypnotic, so all these comparisons are tentative and indirect.

Given that ramelteon and melatonin are similar in efficacy and mechanism, why not just use melatonin as a hypnotic? Melatonin is a standard hypnotic in Europe, where it is regulated as a prescription product. However, in the US, melatonin is an over-the-counter supplement that is particularly vulnerable to quality control issues. When tested, 70% of melatonin products didn't contain the amount on the label, with amounts that varied from 1/5th to 5 times the labeled amount (Erland LAE and Saxena PK, *J Clin Sleep Med* 2017;13(2):275–281). Melatonin's half life (1 hour) is also much shorter than ramelteon's (3 hours), but that problem can be improved with a sustained-release product. If your patient does go the melatonin route, reliable brands include[1]:

- *Sustained release:* Member's Mark (at Sam's Club), Natrol, REMfresh, Source Naturals, and Dr. Wurtman's (which is part SR, part IR).
- *Instant release:* Life Extension, Nature Made, Natrol (at Costco), Swanson, Trader Darwin's (at Trader Joe's), and Walgreens Quick Dissolve

[1]These brands were certified by Consumer Labs or United States Pharmacopeia (USP), or were tested in clinical trials.

When it comes to long-term use, ramelteon has durable benefits, with no tolerance or withdrawal noted in controlled trials lasting up to 6 months and open-label studies up to 1 year. In some studies its benefits built up over weeks to months, which may be due to entrainment of the circadian system with nightly use. Benzodiazepines, and to a lesser extent the z-hypnotics, show some evidence of tolerance and withdrawal effects with long-term use (Neubauer DN, *Neuropsychiatr Dis Treat* 2008;4(1):69–79).

Hypnotics Compared

	Placebo	Minutes greater than placebo				
		Ramelteon	Melatonin	Z-hypnotics	Benzos*	Suvorexant
Falling asleep faster (subjective)	20	4	11	7	14	9
Falling asleep faster (objective)	8	9	6	22	4	11
Increase in total sleep (objective)	18	7	8	14	62	?

*Flurazepam, temazepam, triazolam, and midazolam

Sources: Kuriyama A et al, Sleep Med *2014;15(4):385–392; Ferracioli-Oda E et al, PLoS One 2013;8(5):e63773*

Ramelteon's main advantage is in safety. It did not increase the risk of falls in trials that enrolled patients up to age 93. It is one of a few hypnotics that the *Beers Criteria for Potentially Inappropriate Medication Use in Older Adults* do not flag as problematic in the elderly (the other safer hypnotics in this list include doxepin, suvorexant, lemborexant, and melatonin). Although all hypnotics carry a blanket warning about complex sleep behaviors, such as cooking or driving while asleep, these are not known to occur with ramelteon.

Ramelteon's most common side effect is fatigue, but after a month it did not cause any more next-day sedation than placebo. Like other hypnotics, ramelteon can impair next-day driving. Other possible side effects include nausea, abdominal discomfort, headaches, and paradoxical insomnia (Neubauer, 2008).

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Is Ramelteon an Effective Hypnotic?

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Other benefits

Ramelteon has also been explored in bipolar disorder and delirium. Based on three randomized, placebo-controlled trials (n = 746), ramelteon may lower the risk of relapse into depression in bipolar disorder when started in manic or euthymic states, but this effect is very small—only 1 in 14 patients benefited (Kishi T et al, *Neuropsychiatr Dis Treat* 2019;15:1479–1486).

Both ramelteon and melatonin reduce the incidence of delirium in hospitalized patients at high risk for this syndrome, including postoperative patients. However, melatonin is probably more effective. Evidence supports either 0.5 or 5 mg of melatonin. In high-risk hospitalized patients, melatonin reduced the risk of delirium by 70%–80% (Yang CP et al, *Sleep Med Rev* 2020;50:101235).

How to use it

Ideal candidates for ramelteon include the elderly, those at risk for falls or substance abuse, and patients who are likely to need a long-term hypnotic. The starting dose is the same as the max dose (8 mg qhs) and it can be taken nightly or as needed, about 30 minutes before bedtime. Patients should not take ramelteon too late because doing so might phase-delay the circadian rhythm (ie, turn patients into night owls). Ramelteon is an expensive generic, but most insurers cover it, and its price should fall soon as more generic competitors enter the market.

Patients may have trouble switching from other hypnotics to ramelteon, with its lower potency and lack of rewarding and anxiolytic properties. Cross-tapering may be necessary when changing from some hypnotics.

Ramelteon: At a Glance	
FDA indications	Primary insomnia
Advantages	Safety in elderly, lack of tolerance or abuse
Other uses	Possible benefits in delirium and bipolar depression
Dosage	8 mg nightly or prn
Side effects	Next-day fatigue, headache, nausea
Interactions	Avoid with CYP1A2 inhibitors, like fluvoxamine, which raise ramelteon levels (inducers, like smoking, lower levels); high-fat meals delay its onset by 1 hour
Contraindications	None
Cost	$2–3/tab (expected to drop over next year)

TCPR VERDICT: With their modest benefits, the cardinal rule with sleep medications is to do no harm. Ramelteon fulfills that promise, but it's not as potent as other hypnotics and may not be much better than melatonin.

To learn more, listen to our 12/7/20 podcast, "CBT-Insomnia: A Patient Guide." Search for "Carlat" on your podcast store.

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Expert Interview—Side Effects of Psychotherapy

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Dr. Linden: To start with, it can be burdensome to talk about one's problems and one's own insufficiency. A patient may also go to therapy with an isolated problem, say conflict with their spouse. As they talk about the marital stress, the therapist shifts the focus toward negative events in the patient's history, and soon the patient feels that their whole life has been a mess. That's demoralizing.

TCPR: How common are therapy side effects?

Dr. Linden: Studies that used detailed assessments have shown that 100% of patients experience some burden with psychotherapy. Most of these are not serious or lasting. Relevant side effects that are serious or lasting are reported in about 10% of cases (Linden M and Schermuly-Haupt ML, *World Psychiatry* 2014;13(3):306–309).

TCPR: Are these side effects linked to specific techniques or just to therapy in general?

Dr. Linden: Most are linked to special interventions. Anxiety provocation during exposure therapy can increase anxiety. Early debriefing after a trauma can increase the rate of PTSD. Group therapy can demoralize patients when they hear negative reports from other patients whom they identify with. Even psychoeducation can overwhelm patients in ways that demoralize them and reduce their understanding (Schneibel R et al, *Acta Psychiatr Scand* 2017;136(3):247–258; Linden M and Wasilewski J, *Cogent Psychology* 2019;6(1):1612825).

TCPR: Are some patients at greater risk for side effects?

Dr. Linden: We don't have good data on that, but I think it depends on the therapist-patient match. Patients who are suggestible may be prone to the induction of false memories. Patients with unstable somatic symptoms may be prone to increased anxiety under exposure treatment. Patients with dependent personalities may develop dependency on therapy. (*Ed note:* See table on page 4 for an overview of potential side effects.) The stage of the illness may also play a role in how therapy works. There was a study of CBT in bipolar disorder where they compared it to treatment as usual to see if it could reduce the risk of relapse. It did reduce that risk, but only in the early phase of the illness. The patients

> **"Side effects are common negative effects that occur in all psychotherapies just as they do with most medical therapies. A good therapist doesn't ignore side effects."**
>
> Michael Linden, MD, PhD

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who had been through a dozen or more past episodes actually got worse with the CBT (Scott J et al, *Br J Psychiatry* 2006;188:313–320).

TCPR: I thought it was a good thing to have anxiety during exposure therapy. If that's how the therapy works, how is anxiety a side effect?

Dr. Linden: Currently, exposure therapy does require the induction of anxiety in order to treat anxiety disorders. But this is undoubtedly a burden to the patient. To say this is not a problem is unempathic. If a new treatment came about that helped patients gain better control of their anxiety without frightening them, then the current way of doing things would be unethical and forbidden. There are many examples in medicine where side effects are a deliberate part of the treatment, but they are still side effects, like taking off a breast when fighting cancer. I think that when we acknowledge that anxiety is a side effect to therapy, it can help improve the therapy.

TCPR: Do you suggest talking about side effects openly with the patient?

Dr. Linden: Undoubtedly. A therapist who understands the potential side effects of their therapy will be better able to detect them and find ways to remediate them, or even prevent them from the beginning. A good therapist doesn't ignore side effects.

TCPR: Psychotherapy is already underutilized. Could emphasizing the side effects backfire?

Dr. Linden: You can't ignore the risks of a treatment just because it's underutilized. I know there are countries where coverage for psychotherapy is insufficient, but that should not drive how we talk about these things. In my own country (Germany), all citizens are covered by health insurance, which fully reimburses up to 120 sessions of psychotherapy. Psychotherapists are one of the largest groups of providers in Germany—second to general practitioners—and they treat millions of people. So there's a need for quality assurance, and understanding side effects is part of that.

TCPR: How good are therapists at recognizing when things are going poorly?

Dr. Linden: Several things can get in the way there. In psychotherapy, the therapist is the producer of the treatment. So if something goes wrong, the impression is that the therapist is responsible, which makes it difficult to talk about negative effects of treatment. So we need to distinguish clearly between side effects and malpractice effects.

TCPR: What can be done to improve recognition?

Dr. Linden: We have developed a self-rating scale that covers important areas where side effects can emerge. Our therapists give this to the patient and explain that there can be problems during therapy and that it is good for the patient and the therapist to talk about risks and burdens. Patients love this, and it improves the therapist-patient relationship.

TCPR: Patients often report negative effects of psychotherapy to their psychiatrist or general practitioner instead of their psychotherapist. How should we handle that?

Dr. Linden: This is wonderful. It helps if all co-therapists monitor the course of treatment. All therapists (a patient's psychotherapist, psychiatrist, general practitioner, etc) should work together. They can contact each other and say, "Hey, I have the impression there might be a problem." Because, again, side effects are not a sign of bad treatment. Side effects are negative effects of good treatment.

TCPR: Does following a manual reduce the risk of side effects?

Dr. Linden: No. Manuals may hinder a personalized therapy, and the less personalized it is, the more problems can happen. It does help, however, for the therapist to stick to the rules of the type of therapy that they are doing, which is a little bit different from following a manual step by step.

TCPR: In research, therapy is usually time-limited (eg, 12 sessions). Does that reduce the risk of side effects?

Dr. Linden: No, side effects can occur in all phases of treatment. A treatment that is too short can have side effects because problems have been stirred up but not solved. Treatments that are too long can have side effects because the longer the treatment goes on, the more problems will be aggravated. Patients need personalized treatments.

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

Signs of Psychotherapy Side Effects

Area	Side Effects
Outcomes	• Lack of clear improvement with therapy • Therapy goes on longer than expected • Lack of patient attendance or adherence
Symptoms	• New symptoms emerge during therapy • Symptoms worsen during therapy
Relationships	• Strains in the patient-therapist relationship • Very good patient-therapist relationship • Strains in family relationships • Changes in family relationships • Stigmatization
Employment	• Strains in work relationships • Medical leave from work • Problems in the patient's social network • Any change of life circumstances

Source: Adapted from Linden M, Clin Psychol Psychother *2013;20(4):286–296*

To learn more, listen to our 11/23/20 podcast, "Psychotherapy Side Effects: An Interview With Michael Linden." Search for "Carlat" on your podcast store.

How to Select an SSRI

Chris Aiken, MD. Editor-in-Chief of TCPR. *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.

On March 14, 2012, Lexapro became the last SSRI to lose its patent, closing the book on a quarter century of science and marketing that changed and sometimes confused the way we think about antidepressants. Now that the unpublished studies have come to light and the incentives to favor one drug over another have dried up, it's a good time to take a sober look at what—if anything—really sets the six SSRIs apart.

How well do they work?

Enough independent meta-analyses are available that we can draw some conclusions about where the SSRIs stand in relation to other antidepressants. Judging from head-to-head trials (over 200 in all)[1]:

1. In depression, the SSRIs work about as well as vortioxetine and the tricyclics. Compared to the SNRIs and mirtazapine, they are slightly less effective, but this difference is estimated to affect only 1 in 24 patients.
2. SSRIs work as well as bupropion in depression, even when anxious features are present.
3. In generalized anxiety, social anxiety, and panic disorder, the comparisons are fewer, but SSRIs seem to work about as well as the others—with the possible exception of social anxiety disorder, where the MAOI phenelzine has an unrivaled effect size that's double that of other medications.
4. SSRIs probably work as well as clomipramine in OCD (an earlier meta-analysis found clomipramine more effective, but head-to-head trials and a later meta-analysis have refuted that).

[1]Sources: Papakostas GI et al, *Biol Psychiatry* 2007;62(11):1217–1227; Undurraga J and Baldessarini RJ, *J Psychopharmacol* 2017;31(9):1184–1189; Zimmerman M et al, *J Clin Psychiatry* 2005;66(5):603–610; Davis ML et al, *Expert Opin Pharmacother* 2014;15(16):2281–2291; Ackerman DL and Greenland S, *J Clin Psychopharmacol* 2002;22(3):309–317.

The SSRIs are better tolerated than most antidepressants except vortioxetine and bupropion. Those two are often favored for their cognitive benefits and relative lack of sexual side effects, sedation, and weight gain. So the SSRIs are a good place to start. But which is the most effective?

With a few small exceptions that I'll point out below, none of the SSRIs clearly stand out for their efficacy. Instead, it's their medical risks, drug interactions, and withdrawal problems that set them apart. In those respects, escitalopram, sertraline, and fluoxetine rise to the top, while citalopram, fluvoxamine, and paroxetine are less desirable. I'll explain why as I walk through each of the SSRIs.

Escitalopram and citalopram

Citalopram (Celexa) is a 50/50 mix of R- and S- isomers. Escitalopram (Lexapro) is the purified S- isomer, and its serotonergic effects are 166 times more potent than the R-. These two "-pram" SSRIs were marketed for their relative lack of drug interactions and high selectivity for the serotonin transporter, both of which are true. They are the only SSRIs that don't induce or inhibit the CYP enzymes. This may explain why they have the best evidence for bupropion augmentation (other SSRIs interact with bupropion). But the -prams can be victims of a common drug interaction that, in the case of citalopram, is often a deal breaker.

Citalopram is the SSRI with the highest risk of QTc prolongation (escitalopram is second highest). This risk goes up as the dose increases, and CYP2C19 inhibitors like cimetidine markedly raise citalopram levels. It's a big enough problem that the FDA caps citalopram's dose at 20 mg/day for patients on CYP2C19 inhibitors, poor metabolizers at CYP2C19, and any patient over age 60.

For that reason, I often switch older patients from citalopram to escitalopram. The conversion is imprecise and requires some fine tuning, but a rough approximation is to divide the dose by 3 (eg, 60 mg of citalopram = 20 mg of escitalopram).

Besides being safer in the elderly, escitalopram is also FDA approved down to age 12 in depression, although that approval was based on trials with mixed results and modest benefits. In adults, escitalopram may have a slight efficacy edge over other SSRIs if we believe in network meta-analyses and a handful of head-to-head trials (including against citalopram), but this advantage is minimal at best and illusory at worst (Cipriani A et al, *Lancet* 2018;391(10128):1357–1366).

Sertraline

Sertraline (Zoloft)'s main advantage is safety. Among the SSRIs, it has the most favorable profile in cardiac disease, pregnancy, and breast-feeding (Womersley K et al, *Psychiatr Danub* 2017;29(Suppl 3):629–644). It also has a low chance of upsetting the CYP enzymes as long as the dose is kept below 150 mg/day. Beyond that, it has meaningful inhibition at CYP2D6. This rarely causes problems in depression, where sertraline's benefits plateau beyond 100 mg/day (Hieronymus F et al, *Transl Psychiatry* 2016;6(6):e834).

Fluoxetine

Fluoxetine (Prozac) has a few qualities that patients appreciate. Its long half-life means it has the lowest risk of serotonin withdrawal problems. SSRI withdrawal may not be dangerous, but it stokes fears of addiction that often cause people to avoid psychiatric treatment. Fluoxetine also has less weight gain than the other SSRIs (Uguz F et al, *Gen Hosp Psychiatry* 2015;37(1):46–48). The difference is small, but it may be meaningful for patients with bulimia, where fluoxetine is the only FDA-approved SSRI, and for binge eating disorder, where it has good efficacy evidence. In both those eating disorders, the optimal dose is 60–80 mg/day.

Fluoxetine is usually first line in pediatric depression, where its approval goes down to age 8. Though many drugs have been tried, only a few antidepressants have succeeded in pediatric depression. Those are fluoxetine, escitalopram, citalopram, and sertraline, although they actually have a mix of

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Q&A With the Expert

Brief Therapy During the Medication Visit

Donna Sudak, MD

Professor and Vice Chair for Education and Drexel University College of Medicine. She is the author of four books on psychotherapy, including Combining CBT and Medication: An Evidence-Based Approach *(Wiley, 2011).*

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

TCPR: How does a brief therapy session differ from the 50-minute hour?

Dr. Sudak: What's different is the scope of what you can tackle in those 25–30 minutes. There's a greater need to organize the session and make decisions about what you can take on. For example, trauma is a subject that you'd probably defer to a longer session.

TCPR: How do you manage the patient's expectations?

Dr. Sudak: I explain in the first session that we will want to use the time together in the best way possible. We'll focus on one or two things that the patient wants to address and follow up on any assignments from the last session. I recommend having two clocks so that both the patient and the therapist can keep track of time. I also have patients fill out paper-and-pencil measures like the PHQ-9 and GAD-7 before they come in. That saves time and helps alert me to problems that we may need to focus on.

TCPR: How do you end the session?

Dr. Sudak: I'll let patients know when we have 5 minutes left so we can wrap things up. I ask what they are going to take away from the session and have them write it down. People forget about 50%–70% of what happens at a medical visit, and that is when they are mentally well! Some of my patients tape the session to listen to again in the future.

TCPR: Are there resources you use to help patients keep up the work between sessions?

Dr. Sudak: A lot of people are using apps for that, and a great resource is PsyberGuide (https://onemindpsyberguide.org), which was developed out of Northwestern University and the University of California at Irvine. They rate mental health apps based on the clinical research, the user experience, and how privacy is handled. MoodKit and iPromptU have good cognitive behavioral therapy (CBT) tools, but whatever you recommend, you should try it out yourself first. YouTube is a fabulous resource for exposure therapy because you can access videos that trigger a patient's phobia, like plane turbulence and blood injuries.

TCPR: Do you use printed materials?

Dr. Sudak: Yes, and you need to have those ready in advance. My office is a symphony of manila folders with labels on them. The Oxford Center for Anxiety Disorders and Trauma and PracticeGround have a wealth of resources for therapists and patients, from training videos to therapy handouts (www.oxcadatresources.com; www.practiceground.org). For books, Oxford's *Treatments That Work* series is good, and they have versions for therapists and patients.

TCPR: How do you follow up on assignments?

Dr. Sudak: Homework should always be "no lose," and I set the stage for that before it's even assigned. Are patients confident they can do it? Practicing in session is a good way to test that out. Do they understand the purpose of the assignment? Then I'll get down to specifics with the 4 W's: *Whom* are they going to do it with? *When? Where? What* reminder system are they going to use to remember it? I'll also ask, "Do you see any obstacles to doing it?" If the assignment is to go for more walks, I'll ask, "What if it rains? What if you don't feel like doing it? What has kept you from going for walks up until this point?"

TCPR: What about patients who feel guilty when they don't do the assignment?

Dr. Sudak: If they are feeling guilty about not doing the assignment, I'll want to clarify that: "Well, that's an interesting thought that you're having. What did you think I might be thinking? Are there other possibilities that I might be thinking?" I'll also normalize that it's very hard to engage in new activities, especially during depression.

TCPR: What are your top tips for psychoeducation in a brief session?

Dr. Sudak: I start with, "What do you understand about this problem? From your understanding, what do you need to do to have the best outcome?" You can't assume patients understand their diagnosis, even if they've had it for a long time. They may have gotten psychoeducation during an acute episode when their brain wasn't working well. Psychoeducation also goes best in small, digestible amounts.

TCPR: What are some tips for brief sessions with schizophrenia?

Dr. Sudak: Sometimes a brief session makes more sense in schizophrenia—and also in bipolar disorder—because a patient may be agitated or cognitively impaired and have a hard time with longer sessions. With schizophrenia we often work with hallucinations: What makes them better or worse? Activities that are distracting or absorbing often offer some relief. We want to get the hallucinations to a point where they are kind of a harmless nuisance, like tinnitus.

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Expert Interview—Brief Therapy During the Medication Visit
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Patients don't have to do what the hallucinations tell them to. They can learn rational responses to the content of the hallucinations and verbally speak back to them (and if they are in public, I'll have them talk into a cell phone).

TCPR: What do you focus on with bipolar disorder?

Dr. Sudak: I'll want patients to recognize the early warning signs of a new episode. For mania, that might be credit card spending, how much they are texting, how fast they're driving, and how others say they are talking. Next, we want to make sleep a priority, and I'll look at what gets in the way of sleep. For the depressed phase, I use "action prescriptions." We'll write down important and enjoyable activities that mean something to the patient and use strategies to increase engagement in these activities even when they don't feel like doing them. Mood charting is also helpful, particularly with rapid cycling cases because there we need to see if the episodes are getting less frequent and less severe during the treatment.

TCPR: Is exposure therapy feasible in a brief session?

Dr. Sudak: That's difficult because we need time to debrief after exposure. With OCD we generally start with 90-minute sessions because it takes so long for people's anxiety to go down during those exposures. And you can't expect them to do the exposure outside of session because it's often just too terrifying, especially in the beginning of therapy. Brief sessions may be feasible if they've already had a successful course of exposure therapy or are very motivated. I've seen people with phobias of flying or heights, and once they get the principle down, they run with it.

TCPR: What types of patients are not well suited to brief sessions?

Dr. Sudak: First are patients who have substantial issues with trust. They may need more in the way of relationship building. Some research suggests that patients with personality disorders do better with brief therapy when the focus is on behavioral activation instead of on their way of thinking or relating to others (Coffman SJ et al, *J Consult Clin Psychol* 2007;75(4):531–541). Also, some patients just prefer or need longer sessions; for example, when they aren't taking medication and have a disorder that needs a full course of CBT.

TCPR: So you want to make sure that brief sessions aren't setting the patient up for failure.

Dr. Sudak: Absolutely, and particularly because the instillation of hope is a really important part of what we do. There's an argument that we shouldn't combine treatments—like medication and psychotherapy—because if the combination doesn't work, you've used up two hope items. But if you sequence them, using one at a time, you can still give that injection of hope: "We're doing something new now." That argument hasn't been tested, but there is work on sequencing as a means to enhance durability where clinicians will get people better from depression with medication and then add 8 weeks of group CBT to maintain those gains. It did help people stay well much longer, particularly if they had recurrent episodes in the past (Bockting CLH et al, *J Affect Disord* 2015;185:188–194).

"Any homework that you give to patients should always be 'no lose,' and practicing in session is a good way to test that out. Do patients understand the purpose of the assignment? Then I'll get down to specifics with the 4 W's: Whom are they going to do it with? When? Where? What reminder system are they going to use to remember it?"

Donna Sudak, MD

TCPR: Are there other risks with combining therapy with meds?

Dr. Sudak: With anxiety disorders, patients who undergo CBT while on an antidepressant may need more exposure sessions after they come off the antidepressant. These patients are exquisitely tuned to their internal context, and once they are off the medication, their internal environment feels different. It causes them to be concerned, which turns into hypervigilance and, eventually, panic.

TCPR: So they've learned the CBT in one context, but it doesn't translate into the unmedicated state.

Dr. Sudak: Exactly. That was the finding of a large randomized controlled trial in panic disorder that compared CBT + imipramine to CBT + placebo to imipramine alone. The treatments worked equally well in the acute phase, but after the treatments were stopped, the response rate fell in the ones who took imipramine during CBT (41% vs 26%) or imipramine alone (41% vs 20%) compared to CBT + placebo (41%) (Barlow DH et al, *JAMA* 2000;283(19):2529–2536).

TCPR: Do you warn patients about this?

Dr. Sudak: I'm an informed consent kind of person, so I will tell the patient, "For panic disorder, you could start CBT alone or CBT with an SSRI or just an SSRI. Starting the two together may bring faster results, but the results are more durable if we do the CBT by itself." Some will say, "I'm just gonna take the meds for the rest of my life." And that's certainly a viable option. I don't see it as a moral issue.

TCPR: What about benzos and CBT?

Dr. Sudak: With antidepressants, the problem comes after discontinuation, but benzos can directly interfere with exposure-based CBT. It's hard to do exposure if the patient doesn't get anxious because they are on a benzo. Any sort of avoidance dilutes exposure, and patients can avoid anxiety in all sorts of ways—alcohol, benzos, seeking reassurance, prayers, mantras, or just avoiding the trigger by looking away or distracting.

TCPR: Is the evidence strong enough that you'd avoid exposure therapy if a patient is taking a benzo?

Dr. Sudak: Yes. I'd say, "This is going to be a lot less effective if we do this while you're taking

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Metformin ER Recalled Due to Cancer Risk

Adam Strassberg, MD. Psychiatrist in private practice, Palo Alto, CA.

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

Metformin is often prescribed to our patients to prevent weight gain on antipsychotics, but recently the FDA discovered that large batches of various metformin ER formulations may be contaminated with a carcinogen. Voluntary recalls of metformin ER began in May 2020 and have continued to the present. The result is drug shortages, fear, and an unanswered question: Is it still safe to prescribe metformin?

The cause of the recall is NDMA (N-nitrosodimethylamine), not to be confused with the glutamatergic receptor NMDA (N-methyl-D-aspartate). NDMA is a carcinogen that earlier caused the recalls of several popular angiotensin II receptor blockers and the reflux medication ranitidine. NDMA is a common contaminant found in water and foods, especially cured and grilled meats, dairy products, and vegetables. NDMA is genotoxic, and prolonged exposure to elevated levels increases the risk of cancer. However, a person who takes a drug that contains NDMA at or below the FDA acceptable daily limit (96 nanograms) every day for 70 years is not expected to have an increased risk of cancer.

There are many possible sources of NDMA: the drug's chemical structure, the manufacturing process, the packaging, and even the storage conditions. The exact source of the NDMA impurity for metformin ER remains unknown. To date, FDA testing has not found NDMA in any immediate-release metformin products, so the problem is likely related to the processing of the ER formulation. Branded metformin (Glucophage from Bristol Myers Squibb) has not been affected, although past NDMA recalls have involved both brands and generics.

A searchable list of recalled metformin ER products can be found at this link: www.fda.gov/drugs/drug-safety-and-availability/search-list-recalled-metformin-products

There is also a "good list" of metformin ER products that were tested and found to have no detectable NDMA: www.fda.gov/drugs/drug-safety-and-availability/laboratory-tests-metformin

The recalled medications can be identified specifically by their National Drug Code (NDC) numbers. The NDC is a unique 10-digit, 3-segment number that identifies the labeler (first segment), the product itself (second segment), and the trade package size (third segment). The NDC should be stamped on your patient's medication bottle label or the box it came in. You will also need the lot number, as sometimes only certain lots are recalled. This is either on the label printed by the pharmacy or stamped onto the bottle or package itself, where it may or may not be listed as "LOT." Patients should contact their pharmacy if these identifiers are unclear.

TCPR VERDICT: The safest bet is to stick with instant-release metformin until the full extent and cause of this problem is known. If this causes problematic nausea (the main drawback), patients should take it with food. If you do prescribe metformin ER, guide your patient toward a product on the FDA's "good list."

To learn more, listen to our 11/2/20 podcast, "The Metformin Recall." Search for "Carlat" on your podcast store.

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Expert Interview—Brief Therapy During the Medication Visit

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the benzo," and look for ways to get them off it first. We can actually use CBT to help people get off benzos. The treatment involves exposure work around the physical sensations, relaxation training, and working with cognitions around the medication.

TCPR: How do you lower the benzo during that therapy?

Dr. Sudak: Very slowly—like 10% of the dosage every month. And all the while I give them choices. "Is this a good month?" "Do you want to extend this two more weeks?" The more we partner with people, the better.

TCPR: On the other hand, there are medications that can enhance psychotherapy, like d-cycloserine. Is that ready for clinical practice?

Dr. Sudak: D-cycloserine is a repurposed antibiotic, and a lot of folks are using it to speed up exposure therapy for anxiety disorders and OCD. It's given as a 50 mg dose 30 minutes before the exposure exercise. It had a small effect size (0.25) in a meta-analysis of 21 studies. So it's not the magic everyone's hoped for, but it can speed up the process (Mataix-Cols D et al, *JAMA Psychiatry* 2017;74(5):501–510).

TCPR: Final thoughts?

Dr. Sudak: Brief therapy can add a lot to medication treatment. Outcomes are better for patients, and it also enhances quality of life for the provider because you get to use a lot more of your skill set in the service of helping someone.

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

To learn more, listen to our 11/9/20 podcast, "How to Set Behavioral Goals in the Med Visit: An Interview With Michael Posternak" and our 12/14/20 podcast, "CBT in the Med Visit: An Interview with Donna Sudak." Search for "Carlat" on your podcast store.

Research Updates IN PSYCHIATRY

MEDICATION

Beta Blockers and Depression: The Controversy Revisited

REVIEW OF: Agustini B et al, *J Hum Hypertens* 2020 Jan 30

STUDY TYPE: Cross-sectional

Antihypertensives are among the world's most widely prescribed drugs, but many of them impact pathways associated with depression. Beta blockers have long been believed to cause depression, but most of these studies were carried out decades ago and their findings have been inconsistent. Other classes, like angiotensin-receptor blockers, are associated with lower rates of depression, albeit with weaker evidence.

In this multinational study, researchers examined mood outcomes in 14,195 hypertensive adults over age 65 who did not have heart disease. Depressive symptoms were measured with the self-reported Center for Epidemiological Studies-Depression (CESD-10) scale. Each class of antihypertensive drugs was tested against the other classes and against a group of unmedicated hypertensive patients to see whether any class was associated with an increased risk of clinically significant depressive symptoms.

Patients who took beta blockers were more likely to meet or exceed the clinical cutoff score of 8 on the CESD-10 scale, a sign of clinically significant depressive symptoms, than those who took other antihypertensive drugs. Numerically, 13.4% of patients who used beta blockers showed clinical elevations in depression, whereas between 10.2% and 10.5% of patients who used other antihypertensives showed this elevation. Logistic regression analysis showed that this difference was significant, even when controlling for numerous factors that included gender, age, and smoking history. Other classes of antihypertensives, including angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, and calcium-channel blockers, were not associated with depression.

The researchers also compared the beta blockers based on their selectivity for the beta receptor and their lipophilic properties. Lipophilic medications are more likely to cross the blood-brain barrier, and the more lipophilic beta blockers like propranolol and metoprolol were associated with a higher risk of depression than hydrophilic ones like atenolol. Meanwhile, the less selective beta blockers were less depressogenic, a finding that again favors atenolol.

TCPR'S TAKE

The fact that beta blockers were associated with depression while other antihypertensives were not gives us pause, particularly with the widespread use of propranolol in psychiatry. The increase in depression was small but real in this large geriatric study. Depressed patients with hypertension will do best to avoid beta blockers or, if they must be used, stick with atenolol.

—Sean Ransom, PhD, MP. Dr. Ransom has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

DEPRESSION

Transcranial Direct-Current Stimulation in Depression Reconsidered

REVIEW OF: Razza LB et al, *Depress Anxiety* 2020;37(7):594–608

STUDY TYPE: Meta-analysis of randomized sham-controlled trials

Transcranial direct-current stimulation (tDCS) is a neuromodulatory intervention with putative benefits in depression. The device consists of a headband with two electrodes that delivers a weak electrical current across the brain, generated by a smartphone-sized stimulator. These devices have regulatory approval for depression in Europe, Australia, and Mexico, and have gained popularity in the US among patients who appreciate their low cost (around $500), limited side effects, and ability to self-administer the treatment. tDCS is well tolerated with commonly reported side effects of tingling sensations, headache, fatigue, and scalp erythema. Psychiatrists, however, have been reluctant to adopt tDCS because of concerns over efficacy. The available studies have been few with small sample sizes and mixed results, including one where escitalopram outperformed tDCS. This new meta-analysis aggregated data from available tDCS trials to assess its efficacy in depressive symptoms.

The authors identified 23 randomized, sham-controlled trials with a total of 1,092 patients who were assigned to either active or sham tDCS. Two of the studies were large (> 100 patients), three included bipolar depression, and eight focused on treatment-resistant depression. All studies used anodal tDCS, which uses a positive-ion current as opposed to the negative ions of cathodal stimulation. Anodal stimulation depolarizes the neurons while cathodal stimulation hyperpolarizes the neurons. The treatments were delivered over the left dorsolateral prefrontal cortex at current intensities between 0.5 and 2.5 mA with subjects receiving 5 to 20 treatments lasting 10 to 30 minutes per session. The primary outcome was the effect size for depression scores. Secondary analyses included response and remission rates.

Compared to sham, the active tDCS group showed an improvement in depression scores with a moderate effect size (0.46). Response (33.3% vs 16.56%; number needed to treat of 6) and remission (19.12% vs 9.78%; number needed to treat of 11) rates were also better with active tDCS.

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Research Updates

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The main limitation of these findings is the difficulty of lumping together many small studies, each with its own design that could influence the sham or placebo response. Another limitation was that most studies evaluated outcomes after a few weeks, but the full effects of tDCS may not be seen for a few months.

TCPR'S TAKE

tDCS is a promising treatment for depression, but we still need large, well-designed controlled trials to be confident in its effects. While we await more evidence, we can consider tDCS selectively for patients who decline, don't tolerate, or don't respond adequately to antidepressants. tDCS is also a convenient, well-tolerated option for patients who are wary of other neuromodulatory interventions like ECT and TMS.

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

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How to Select an SSRI

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positive and negative results (Cipriani A et al, *Lancet* 2016;388(10047):881–890).

The reason to avoid fluoxetine is its drug interactions. As a potent inhibitor at CYP2D6 and 2C19, fluoxetine raises levels of many medications, including propranolol and antidepressant augmenters like aripiprazole, brexpiprazole, risperidone, bupropion, and the tricyclics (and it does so for up to 6 weeks after it is stopped). In some cases, fluoxetine can render medications less effective by preventing their conversion to active metabolites at CYP2D6 (eg, tamoxifen, tramadol, hydrocodone).

Fluvoxamine

Fluvoxamine (Luvox) is approved only for OCD in the US, though in other countries it is licensed for depression and social anxiety disorder. In those disorders it works about as well as the other SSRIs, but there are two qualities that make it less favorable: high withdrawal symptoms and drug interactions. It is a potent inhibitor at CYP1A2, 3A4, 3A5, and 2C19, which can cause significant problems if it raises the levels of clozapine, clomipramine, alprazolam, flibanserin, ramelteon, theophylline, and warfarin.

Paroxetine

Paroxetine (Paxil) is the problem child of the SSRIs. It has the highest risk of serotonin withdrawal, birth defects, suicidality in children, weight gain, and fatigue (Nevels RM et al, *Psychopharmacol Bull* 2016;46(1):77–104). Its anticholinergic effects make it less favorable in the elderly, and it is the only SSRI that has been linked to dementia risk. As a strong CYP2D6 inhibitor, paroxetine can raise many medication levels or, like fluoxetine, render tamoxifen and some opioids ineffective.

Paroxetine has a reputation as the best SSRI for anxiety, perhaps because it is FDA approved in more anxiety disorders than its competitors. However, its anxiolytic effects are generally less than or equal to other SSRIs. In depression, anxious features do not predict who will respond to paroxetine (Sugarman MA et al, *PLoS One* 2014; 9(8):e106337; Sanchez C et al, *Int Clin Psychopharmacol* 2014;29(4):185–196).

What is there to redeem paroxetine? Like any medication, some patients respond well to it, but it's impossible to predict who they are.

TCPR VERDICT: Escitalopram and sertraline are good all-around SSRIs. Sertraline is the go-to in pregnancy and heart disease, while fluoxetine is first choice in childhood depression. Fluoxetine's relative lack of withdrawal problems makes it a friendly choice for many patients, but its drug interactions can hold it back.

To learn more, listen to our 11/16/20 podcast, "The Rise and Sudden Fall of Zimelidine, the First SSRI." Search for "Carlat" on your podcast store.

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The SSRIs Ranked

First Line	**Escitalopram**	Doesn't cause CYP drug interactions but can fall victim to them. Approved in children down to age 12.
	Fluoxetine	Relatively low risk of withdrawal symptoms and weight gain. Only SSRI with approval in bulimia. Best-studied SSRI in children. High risk of drug interactions.
	Sertraline	Favored in cardiac disease and pregnancy. Few drug interactions below 150 mg/day.
Second Line	**Citalopram**	Highest risk of QTc prolongation. Low risk of CYP drug interactions. Dose capped to 20 mg/day in patients over age 60.
	Fluvoxamine	Indicated only in OCD (in children and adults). High risk of drug interactions. Second worst for withdrawal problems.
	Paroxetine	Highest risk of withdrawal problems, fatigue, sexual dysfunction, weight gain, cognitive impairment, suicidality in children, and birth defects. Strong CYP2D6 drug interactions.

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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/

This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Learning Objectives (LO) are listed on page 1.

1. Compared to placebo, how much faster does ramelteon help patients with primary insomnia fall asleep? (LO #1)
   [ ] a. No difference [ ] b. 4–9 minutes [ ] c. 10–19 minutes [ ] d. 20–25 minutes

2. Which is the only FDA-approved SSRI for bulimia? (LO #2)
   [ ] a. Sertraline [ ] b. Escitalopram [ ] c. Citalopram [ ] d. Fluoxetine

3. In a recent meta-analysis assessing the efficacy of transcranial direct-current stimulation (tDCS) as a potential treatment for depressive symptoms, what was the main limitation? (LO #4)
   [ ] a. Difficulty of combining data from many small studies with their own designs
   [ ] b. Differences in the severity of depression symptoms of subjects between studies
   [ ] c. Differences in where tDCS was delivered to the brain
   [ ] d. Differences in use of anodal vs cathodal tDCS

4. According to Dr. Linden, serious or lasting psychotherapy side effects occur in what percentage of patients? (LO #3)
   [ ] a. < 1% [ ] b. 5% [ ] c. 10% [ ] d. 20%

5. What is the optimal starting dose for ramelteon? (LO #1)
   [ ] a. 2 mg bid, dosed in the morning and evening
   [ ] b. 4 mg qhs nightly
   [ ] c. 8 mg qhs nightly
   [ ] d. 16 mg qhs, split into 2 doses (morning and evening)

6. In a recent meta-analysis examining the efficacy of tDCS in depressive symptoms, what was concluded about the active tDCS group compared to the sham tDCS group? (LO #4)
   [ ] a. The two groups had equal improvement in depression scores
   [ ] b. The active tDCS group showed an improvement in depression scores with a moderate effect size
   [ ] c. The active tDCS group had lower remission rates
   [ ] d. The active tDCS group showed an improvement in depression scores with a large effect size

7. According to Dr. Sudak, patients who undergo cognitive behavioral therapy (CBT) while on an antidepressant often require fewer exposure sessions after they come off the antidepressant. (LO #3)
   [ ] a. True [ ] b. False

8. Which SSRI has the highest risk of serotonin withdrawal, weight gain, and fatigue? (LO #2)
   [ ] a. Fluvoxamine [ ] b. Escitalopram [ ] c. Paroxetine [ ] d. Citalopram

9. According to a 2020 study, based on lipophilicity and selectivity, which beta blocker under investigation was associated with the lowest risk of depression? (LO #4)
   [ ] a. Metoprolol
   [ ] b. Atenolol
   [ ] c. All of the beta blockers investigated had the same risk of depression
   [ ] d. Propranolol

10. According to Dr. Sudak, when conducting brief psychotherapy sessions, what type of emphasis may be best suited for patients with personality disorders? (LO #3)
    [ ] a. The patient's personal relationships
    [ ] b. The patient's way of thinking
    [ ] c. Any concurrent substance use
    [ ] d. Behavioral activation

11. According to studies, which antidepressants are better tolerated than SSRIs in terms of cognitive benefits and lack of sexual side effects, sedation, and weight gain? (LO #2)
    [ ] a. Bupropion and duloxetine
    [ ] b. Duloxetine and venlafaxine
    [ ] c. Bupropion and vortioxetine
    [ ] d. Levomilnacipran and vortioxetine

12. According to a 2020 study, in terms of the percentages of patients who showed clinical elevations in depression, what was the difference between patients who used beta blockers versus patients who used other antihypertensives? (LO #4)
    [ ] a. A lower percentage of patients who used beta blockers showed clinical elevations in depression
    [ ] b. There was no percentage difference between the two groups
    [ ] c. There was a significant difference between the higher percentage of patients who used beta blockers and the lower percentage of patients who used other antihypertensives
    [ ] d. There was a significant difference between the lower percentage of patients who used beta blockers and the higher percentage of patients who used other antihypertensives

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In Brief

Chemical Exposures

Two recent studies add to the mounting evidence that environmental toxins deserve a place in the bio-psycho-social-spiritual model. The first study correlated ADHD symptoms with exposure to endocrine-disrupting chemicals found in plastics, pesticides, and processed food. Based on urine samples collected from 205 adolescents, they found a strong correlation between levels of these chemicals and ADHD symptoms as rated by parents, teachers, and teens. The correlation does not prove causation, although it did hold up after adjusting for cofounders and is supported by earlier research in adults. These are the same chemicals that are linked to early puberty and cancer, and they are among the reasons we're advised to avoid microwaving in plastic (Shoaff JR et al, *JAMA Netw Open* 2020;3(8):e2015041).

The second study was a meta-analysis of ultra-processed food consumption from 23 cross-sectional and prospective cohort studies. Rates of depression were 20%–30% higher in people whose diet was packed with ultra-processed foods, and rates of metabolic syndrome were about double. Again, while causation is only implied here and not proven, there are many plausible pathways by which processed foods might impair brain function (Pagliai G et al, *Br J Nutr* 2020 Aug 14;1–11).

Ultra-processed foods include the usual suspects—packaged snacks, sodas, and fast and frozen foods—as well as deli meats, condiments, and mass-produced breads. Learn more in our *60 Second Psych* Carlat podcasts from 10/31/20, 11/4/20, and 11/7/20.