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Chris Aiken, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Bipolar II

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

1. Evaluate the effectiveness of oxcarbazepine as a treatment for bipolar II disorder.
2. Identify the differences in diagnosing and treating bipolar II vs bipolar I disorder.
3. Summarize some of the current research on psychiatric treatment.

Oxcarbazepine: Tolerable, but Effectiveness Still Debated

You are selecting a mood stabilizer for a 29-year-old woman with mania. If it works, she'll need to take it long term, but with adherence rates hovering around 50% in this illness, that's not a likely prospect. The FDA-approved options are not very high on tolerability, but what about oxcarbazepine?

Oxcarbazepine (Trileptal) is often used in bipolar disorder in place of its FDA-approved cousin, carbamazepine (Equetro, Tegretol). The thinking is that oxcarbazepine is safer, better tolerated, and less prone to drug interactions. However, those assumptions don't quite hold up to the facts, and there's a pile of unpublished research that raises questions about whether oxcarbazepine even works.

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Highlights From This Issue

In bipolar disorder, oxcarbazepine is slightly better tolerated than carbamazepine, but less effective. While its medical risks are different, they are by no means safer than carbamazepine's. Its drug interactions can be a problem as well.

On average, higher doses of second-generation antidepressants do not bring greater recoveries in major depression, but they do cause a steep increase in side effects and dropouts.

A new antipsychotic and a new sleep medication are reviewed.

Q&A With the Expert

Psychopharmacology in Bipolar II
Tammas Kelly, MD

Psychiatrist in private practice in Fort Collins, CO. Author of The Art and Science of Thyroid Supplementation for the Treatment of Bipolar Depression *(2018)*

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

TCPR: You've carved out a unique practice with difficult-to-treat bipolar disorders. Tell us about the patients you see.
Dr. Kelly: I see a lot of bipolar II and "softer bipolar." Clinically these patients have chronic depression, often mixed with hypomanic symptoms. Nearly all have tried multiple antidepressants that didn't work, stopped working, or made their mood worse. They don't look like the textbook bipolar case. It's hard to see "two poles" because the hypomanic symptoms are usually mixed in with depression, anxiety, and irritability. Many had their last clear hypomanic episodes 20 years ago. Some might even be classified in the DSM-5 as unipolar, under the new category "Major depression with mixed features."
TCPR: So you're not seeing the textbook case. Are these rare cases?
Dr. Kelly: No. It's actually the patients with classic, euphoric hypomania who are relatively rare. So it's easy to miss a case of bipolar if you're just looking for euphoria. You have to look for other clues—like family history,

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Oxcarbazepine: Tolerable, but Effectiveness Still Debated

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Oxcarbazepine, carbamazepine: What's the difference?

Oxcarbazepine and carbamazepine differ by only a single carbonyl bond, so it seems intuitive that they should have similar clinical effects. However, small differences like this can sometimes be profound. For example, imipramine and chlorpromazine differ only in two bonds, but the former is an antidepressant and the latter an antipsychotic. Oxcarbazepine and carbamazepine actually target different sodium channels, so there's reason to doubt that they have overlapping clinical effects.

Does oxcarbazepine work?

Most experts say that oxcarbazepine does not treat bipolar disorder because it failed to work in two placebo-controlled trials. However, there are problems with those studies. The first was small (n = 55) and tested oxcarbazepine's long-term preventative effects as an add-on to lithium. Lithium is very effective in the maintenance phase, so it may have washed out any benefits of the additional oxcarbazepine (Vieta E et al, *Int J Neuropsychopharmacol* 2008;11(4):445–452).

The second study evaluated oxcarbazepine's acute antimanic effects in children and adolescents. It is the only large study of oxcarbazepine in bipolar disorder (n = 116), but only 62% of the subjects completed the study. To the drug's credit, there were more dropouts in the placebo group, and oxcarbazepine outperformed placebo with a response rate of 42% vs 26%, but the better performance was not statistically significant (Wagner KD et al, *Am J Psychiatry* 2006;163(7):1179–1186).

Another flaw of the pediatric study is that it recruited from 20 research sites. Too many sites can cause studies to fail. When each site has only a handful of subjects, those subjects tend to get more attention, which enhances the placebo response. It's also harder to keep the methods consistent across each site. The same authors conducted a similar multisite study of valproate in pediatric mania, and the active treatment failed to separate from placebo there as well.

Oxcarbazepine performed better when it was compared to other mood stabilizers instead of to a placebo. In nine studies involving 318 subjects, it worked as well as lithium, valproic acid, carbamazepine, and haloperidol in mania and mixed states (seven studies), hypomania (one study), or the maintenance phase (one study) (Vasudev A et al, *Cochrane Database Syst Rev* 2011;12:CD004857). The best results were achieved when oxcarbazepine was used to augment lithium in mania, where it actually outperformed carbamazepine.

The main limitation of these studies is that they were small and lacked a placebo control. Without a placebo, we don't know if the improvements in both groups were due to nonspecific factors. Simply entering the structured setting of a controlled trial can improve manic symptoms.

Oxcarbazepine may have a role in specific symptoms. For example, it reduced impulsivity and aggression in small, placebo-controlled studies of patients with and without bipolar disorder (Mattes JA, *J Clin Psychopharmacol* 2005;25(6):575–579).

What about safety?

The hope of oxcarbazepine is that it's close enough to carbamazepine to treat bipolar, but different enough to be safer and more tolerable. There's a grain of truth to that.

Oxcarbazepine was about 20% less likely to cause side effects than carbamazepine in the studies that compared the two drugs, both in epilepsy and bipolar disorder. The side effects it did cause were similar to those seen with carbamazepine: headache, dizziness, somnolence, nausea, and rash. Side effects are most likely to occur in the first 4 weeks of treatment and tend to be transient.

In terms of safety, oxcarbazepine is better in some respects and worse in others. It has a higher risk of hyponatremia. The

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How to Use Oxcarbazepine in Bipolar Disorder

Dose in bipolar II	*For hypomania or mild mixed features.* Start ½ of 150 mg qhs, raise by 75 mg every 4–7 days, target: 300–600 mg qhs
Dose in bipolar I	*For mania or mixed states as an adjunct to a traditional mood stabilizer (especially lithium).* Start 150–300 mg qhs, raise by 150–300 mg every 4–7 days, target 600–2100 mg (usual 900–1200 mg; give part of dose in morning if ≥ 1200 mg/day)
XR form (Oxtellar)	Expensive (monthly cost of $1,100 vs. $20 for instant release). May improve side effects due to lower peak levels, but usually unnecessary for mood disorders. Raise dose by 20% when converting from IR to XR at levels of ≥ 1200 mg/day; otherwise the conversion is 1:1
Half-life	9 hours
Common side effects	Headache, dizziness, somnolence, and nausea
Major risks	Hyponatremia, severe allergic rash
Drug interactions	Potent CYP3A4 inducer at doses ≥ 1200 mg/day, which can lower levels of birth control pills and multiple psychiatric medications (antipsychotics, mirtazapine, trazodone, vilazodone, vortioxetine, modafinil, zaleplon, zolpidem, alprazolam and other benzos)

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Oxcarbazepine: Tolerable, but Effectiveness Still Debated

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risk of severe hyponatremia (Na < 125) is 1.3% for oxcarbazepine vs 0.1% for carbamazepine; for mild, it's 30% vs 15%. Severe hyponatremia can lead to seizures, coma, and death. Annual electrolyte checks will catch some cases of hyponatremia in the early stages but miss the majority, so warn patients of the signs: malaise, nausea, dizziness, and headache.

On the other hand, the aplastic anemia and agranulocytosis seen with carbamazepine (at a rate of 1 in 100,000) are not seen with oxcarbazepine. Both medications carry a risk of rash, Stevens-Johnson syndrome, and elevated liver enzymes. Patients of Asian descent should be screened for the HLA-B*1502 allele, as this confers an increased risk of severe skin reactions with both carbamazepine and oxcarbazepine.

Oxcarbazepine is also thought to lack the problematic drug interactions of carbamazepine. As a potent inducer at CYP3A4, carbamazepine renders many medications nearly ineffective, including antidepressants and antipsychotics. However, oxcarbazepine also induces CYP3A4 in the higher dose range that's usually needed for mania (≥ 1200 mg/day). It's a less potent inducer than carbamazepine—about 50% less so—but this is no reassurance when it comes to the CYP3A4 interaction with the highest stakes: oral contraceptives.

More practical tips on how to use oxcarbazepine are in the table on page 2.

TCPR VERDICT: Oxcarbazepine sits on a pile of flawed studies in bipolar disorder. We can't say that it works, but we can't rule it out. Avoid using it as the sole mood stabilizer, particularly in bipolar I disorder. It may have a role as an augmentation therapy in mania and mixed states, but even then it is third line. Oxcarbazepine has slightly fewer side effects and drug interactions than carbamazepine, but it's not safer—hyponatremia is common and dangerous when taking oxcarbazepine.

To learn more, listen to our 3/9/20 podcast, "The Choice: Oxcarbazepine or Carbamazepine in Bipolar." Search for "Carlat" on your podcast store.

Expert Interview

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treatment response, and mixed features—otherwise, most bipolar II patients just look like chronic relapsing depression. Patients with bipolar II spend 1.3% of their lives in pure hypomania and about 50% of their lives in depression, according to a 13-year study with weekly mood ratings (Judd LL et al, *Arch Gen Psychiatry* 2003;60(3):261–269). Patients rarely come in when they are euphoric. They might come in when the hypomania turns irritable or anxious, or their family will bring them in if the hypomania is causing trouble.

TCPR: So their hypomanic symptoms are more often mixed with depression. What does a mixed state look like in bipolar II?

Dr. Kelly: Patients are dysphoric, irritable, and/or anxious.

TCPR: How is "dysphoria" different from depression?

Dr. Kelly: Depression means "low mood," but dysphoria is an intense state of distress, unease, or dissatisfaction. Many of these patients are suicidal. Mixed states carry a higher risk of suicide than depression (Rosenblat JD and McIntyre RS, *CNS Spectr* 2017;22(2):141–146). These patients complain of anxiety, insomnia, and racing thoughts. They're often close to losing something big in their life, like family or job. Many are using large amounts of alcohol or marijuana.

TCPR: What do we know about treatment for bipolar II and mixed states?

Dr. Kelly: Not enough. These are difficult cases because most of the clinical trials were done in bipolar I. Very few included bipolar II patients, and even fewer involved exclusively bipolar II. The quetiapine (Seroquel) studies included bipolar II, but most of the other atypicals, like lurasidone (Latuda), did not. Quetiapine can work in bipolar II depression, but the weight gain and sedation are major drawbacks. The company that makes cariprazine (Vraylar) did a study in bipolar II depression in 2009, but it was negative and never got published until last month (Yatham LN et al, *Int Clin Psychopharmacol* Feb 13 2020 [Epub ahead of print]). After that, the company focused on bipolar I, and that's what cariprazine's recent FDA approval in bipolar depression was based on. In my own practice, I use cariprazine in bipolar II depression and see good results.

TCPR: How do you dose cariprazine in bipolar II?

Dr. Kelly: I start at 1.5 mg every other day and wait at least 4 weeks before increasing it.

TCPR: Is it reasonable to apply the bipolar I studies to bipolar II?

Dr. Kelly: That's what many people do, but there are problems with that approach. These are not the same illnesses. They are related genetically, but so are schizophrenia and bipolar I. One thing I've learned is that small doses work better in bipolar II for most medications. Take aripiprazole. It failed to treat bipolar I depression in the large trials, where the average dosage was 15–18 mg/day, but in a post-hoc analysis there was statistically significant improvement among patients in the lower dosage range (5–10 mg/day) (Yatham LN, *J Affect Disord* 2011;128:S21–S28). I published a case series showing benefits at or below 5 mg/day in 212 patients with bipolar II and bipolar NOS, including 23 who had spontaneous off-on-off-on trials that confirmed the benefits. We see this "U-shaped curve" pattern with other medications as well. In unipolar depression, nortriptyline works best with blood levels between 50 and 139 ng/mL, but when you raise the dose beyond that, the efficacy tends to go down (Kelly T and Lieberman DZ, *J Clin Psychopharmacol* 2017;37(1):99–101).

TCPR: What medication do you usually start with in bipolar II?

Dr. Kelly: I start with lamotrigine; it is well tolerated, treats depression—which is what bipolar II patients struggle with—and has preventative benefits. Getting bipolar II patients out of depression isn't enough: We need medications that prevent relapse, and since they'll need that medication long term, choosing tolerable medications is important.

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Expert Interview

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TCPR: Lamotrigine is FDA approved for prevention of new episodes, but there's been some debate about whether it can treat acute depression.

Dr. Kelly: Yes, it got a bad rep early on because the company sponsored five trials in acute bipolar depression and most of them were negative. When all five were meta-analyzed together, there was a real effect, although the number needed to treat (NNT) was larger than we would like: 11 (Geddes JR et al, *Br J Psychiatry* 2009;194(1):4–9). But there are a few caveats to consider here. First, those early trials lasted around 7 weeks, and it takes 4 weeks to reach a therapeutic dose with lamotrigine, so they may have been too short. Lamotrigine treats acute depression when it's given enough time, as was shown in the 12-week CEQUEL trial (Geddes JR et al, *Lancet Psychiatry* 2016;3(1):31–39). Second, most of the lamotrigine trials excluded bipolar II patients, but lamotrigine actually worked better in the trials that included bipolar II (Parker G and McCraw S, *Acta Psychiatr Scand* 2015;132(5):345–354). Lamotrigine is rarely enough by itself, however, and I often use it in conjunction with other medications like oxcarbazepine, aripiprazole, and thyroid augmentation.

TCPR: In this issue we review oxcarbazepine in bipolar disorder. The studies are a mix of positive and negative. What's been your experience with it?

Dr. Kelly: I've used oxcarbazepine in 1477 patients, and nearly all of them had bipolar II or bipolar NOS. I wouldn't rely on it alone in bipolar I. Oxcarbazepine is sometimes useful to augment other mood stabilizers in bipolar I, but by itself it's not very useful for mania like carbamazepine can be.

TCPR: What role does oxcarbazepine have in bipolar II?

Dr. Kelly: It's a gentler but weaker mood stabilizer. Stronger ones like valproate—and to some degree lithium and carbamazepine—can flatten bipolar II patients and even make them feel depressed, especially at high doses. Oxcarbazepine can do that as well, but usually only in high doses, so when I use it in bipolar II I stick with the lower dose range. Most people respond well to 450–600 mg/day, but this is in the context of polypharmacy. I'd never expect oxcarbazepine alone to do everything in bipolar II. Often I'll use it in addition to lamotrigine.

"It's easy to miss a case of bipolar II if you're just looking for euphoria. You have to look for other clues—like family history, treatment response, and mixed states—otherwise, most bipolar II patients just look like chronic relapsing depression."

Tammas Kelly, MD

TCPR: What symptoms does oxcarbazepine help in bipolar II?

Dr. Kelly: Anxiety, racing thoughts, and most of the hypomanic symptoms. It's surprisingly good at treating anxiety. It can be somewhat helpful for depressive symptoms as well. It's not very sedating, but it can help insomnia indirectly by treating hypomania and agitation.

TCPR: When patients get better on oxcarbazepine, do you try to taper it off, or do you keep it going for prevention?

Dr. Kelly: I usually keep it going. It does have preventative benefits, and when a medication works well in bipolar II, it's best to keep patients on it unless they are having difficult side effects. Otherwise, the problems it treats—mixed states, hypomania, and anxiety, plus some mild benefits in depression—tend to come back.

TCPR: What kind of side effects do you run into?

Dr. Kelly: The biggest one is low sodium—about 1% to 2% of patients on oxcarbazepine develop that. I don't check sodium levels routinely because the problem is so idiosyncratic that routine tests won't catch it. Sedation can also be a problem, but that's rare if the dose is all taken at bedtime. About 1 in 200 patients become more depressed on it, which I see with other mood stabilizers as well. The rate is too low to be picked up in randomized controlled trials, but those trials are designed to test efficacy, not rare side effects.

TCPR: How can a mood stabilizer cause depression?

Dr. Kelly: Possibly it strips away the hypomanic symptoms without treating the depression. I don't have any proof of that. What I do see is that a lot of patients who report depression on a mood stabilizer like oxcarbazepine eventually end up doing well on it. So we can't always judge the long-term benefits from the short-term response in bipolar.

TCPR: How do you titrate oxcarbazepine?

Dr. Kelly: I usually start with ½ of 150 mg at night and then raise it by 75 mg every week for 3 weeks. Then I'll adjust it based on the patient's response. My titration is lower and slower than what most physicians use, but I'm looking for the sweet spot, which is usually between 300 and 600 mg/day in bipolar II. It's easier to find that with slow titration. Oxcarbazepine can be hard to tolerate at higher doses, and it starts to have drug interactions similar to carbamazepine when it goes above 1200 mg per day, but that's not why I keep it low in bipolar II. I just find that lower doses work best for these patients.

TCPR: Do you ever see a role for carbamazepine in bipolar II?

Dr. Kelly: Definitely. You might assume that if patients don't tolerate oxcarbazepine, they won't tolerate carbamazepine, but some do. So sometimes I'll use carbamazepine if they do well on oxcarbazepine but can't tolerate it. Other times patients need carbamazepine for its stronger antimanic properties. But it's a small minority of bipolar II patients that need carbamazepine.

TCPR: Earlier you said that there wasn't much research to guide treatment in bipolar II, so I take it that what you've shared is based on your clinical experience.

Dr. Kelly: Yes. What I've said is guided by research as much as possible, but it's really evolved in a Darwinistic fashion out of my practice. My patients are fairly typical for bipolar II, and my practice is not that unique as bipolar II is

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News of Note

Lumateperone and Lemborexant

Two new psychiatric medications were approved in the final days of 2019. One is the first of its kind, an antipsychotic with minimal dopaminergic blockade: lumateperone (Caplyta). The other is lemborexant (Dayvigo), a variation on the hypnotic suvorexant (Belsomra).

Lumateperone (Caplyta)

Though classified as an atypical antipsychotic, lumateperone is unusual in that it treats psychosis without significant dopamine (D_2) blockade. Its receptor occupancy at D_2 is 39%, while most antipsychotics occupy D_2 at 60% and above (Vanover KE et al, *Neuropsychopharmacology* 2019;44(3):598–605). The other exceptions to this rule are clozapine and quetiapine—both of which are light on dopamine blockade and heavier on serotonergic (5-HT2A) antagonism—and pimavanserin (Nuplazid), an inverse agonist at 5-HT2A that is approved for Parkinson's psychosis.

Besides its low affinity for D_2, lumateperone also works as a partial agonist at D_2 when it binds there. In that respect it resembles aripiprazole, brexpiprazole, and cariprazine, although its agonist activity was significantly less than aripiprazole and brexpiprazole in a head-to-head comparison (Zhang L and Hendrick JP, *Matters* 2018;10.19185).

Lumateperone's mechanism of action predicts a favorable tolerability profile, and the available studies back that up. Sedation is the main risk, affecting 1 in 8 patients (based on number needed to harm). Those numbers improved when the company wisely switched from morning to evening dosing in their later studies. Other common side effects include nausea (9% vs 5% on placebo), dry mouth (6% vs 2%), and dizziness (5% vs 3%). Notably absent are extrapyramidal side effects, akathisia, weight gain, metabolic disturbances, and prolactinemia in studies lasting up to 1 year.

Lumateperone improved symptoms of schizophrenia in three out of four randomized controlled trials. The negative trial was deemed a "failed trial" due to a high placebo response rate (specifically, it included a risperidone arm that also failed to separate from placebo). When compared to risperidone 4 mg/day in another trial, lumateperone worked equally well on positive psychotic symptoms and slightly better on negative symptoms (Corponi F et al, *Eur Neuropsychopharmacol* 2019;29(9):971–985; Citrome L, *CNS Spectr* 2016;21(S1):1–12). That's good news, as risperidone usually ranks alongside olanzapine as one of the more effective atypicals. On the other hand, lumateperone's benefits were less impressive in a large placebo-controlled trial where it had only a small effect size (0.3) in schizophrenia (Correll CU et al, *JAMA Psychiatry* 2020; Jan 8).

Lumateperone is given once daily as a 42 mg capsule without titration. Lower (28 mg) and higher doses (84 mg) did not work. Taking it with food may improve tolerability by dampening and delaying the peak blood level, but this is not necessary for absorption, unlike drugs such as lurasidone and ziprasidone. It is metabolized through CYP3A4 and isn't known to have active metabolites. A long-acting injectable is in development, and FDA approval is being pursued for bipolar depression and behavioral disturbances in dementia.

TCPR'S TAKE

After 60 years of development, we've yet to see an effective antipsychotic that didn't come with serious risks. Contenders have risen and fallen: risperidone, aripiprazole, ziprasidone. Lumateperone is the latest to claim that title, and time will tell if it lives up to those expectations. In terms of efficacy, its four trials are a mix of good and bad news, and its real-world benefits are yet to be tested.

Lemborexant (Dayvigo)

Lemborexant attempts to improve on some of the pitfalls with sleep medications (especially the so-called "z-hypnotics" like zolpidem): falls, traffic accidents, memory impairment, and next-day sedation, problems that pose particular risks in the elderly. Like suvorexant (Belsomra), lemborexant works by blocking orexin, a neuropeptide that increases wakefulness and appetite. Both are competitive antagonists at the orexin 1R and 2R receptors. One difference is that lemborexant has an active metabolite, M10, which has similar effects on the orexin receptors.

Lemborexant was effective in two

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Orexin Antagonists for Insomnia

	Lemborexant (Dayvigo)	Suvorexant (Belsomra)
Dosage	5–10 mg qhs (5, 10 mg tabs)	5–20 mg qhs (5, 10, 15, 20 mg tabs)
Directions	Take immediately before going to bed	Take within 30 minutes of going to bed
Time to safe driving	7 hours	7 hours
Side effects	Daytime fatigue, headache, nightmares, complex sleep behaviors, sleep paralysis, hypnagogic hallucinations	Same as lemborexant (at left); reports of increased cholesterol that was mild but dose dependent (1–2 mg/dL)
Food effects	High-fat meal delays absorption by 2 hours	High-fat meal delays absorption by 1.5 hours
Pharmacokinetics	Tmax 1–3 hours; half-life 17–19 hours	Tmax 2 hours (0.5–6 hours); half-life 15 hours (10–22 hours)
Interactions	Levels raised by CYP3A4 inhibitors (nefazodone, ciprofloxacin, diltiazem, erythromycin, verapamil, grapefruit juice) Levels lowered by CYP3A4 inducers (eg, carbamazepine, phenytoin), but with lemborexant these inducers will produce an active metabolite	
Contraindications	Narcolepsy (which is caused by a mutation in the orexin receptor)	
Advantages over z-hypnotics	Safer in elderly; lower risk of falls, morning sedation, and addiction; efficacy is likely to vary by patient, with some preferring orexin antagonists while others preferring a z-hypnotic	

Research Update IN PSYCHIATRY

DEPRESSION

Optimal Antidepressant Doses in Major Depression

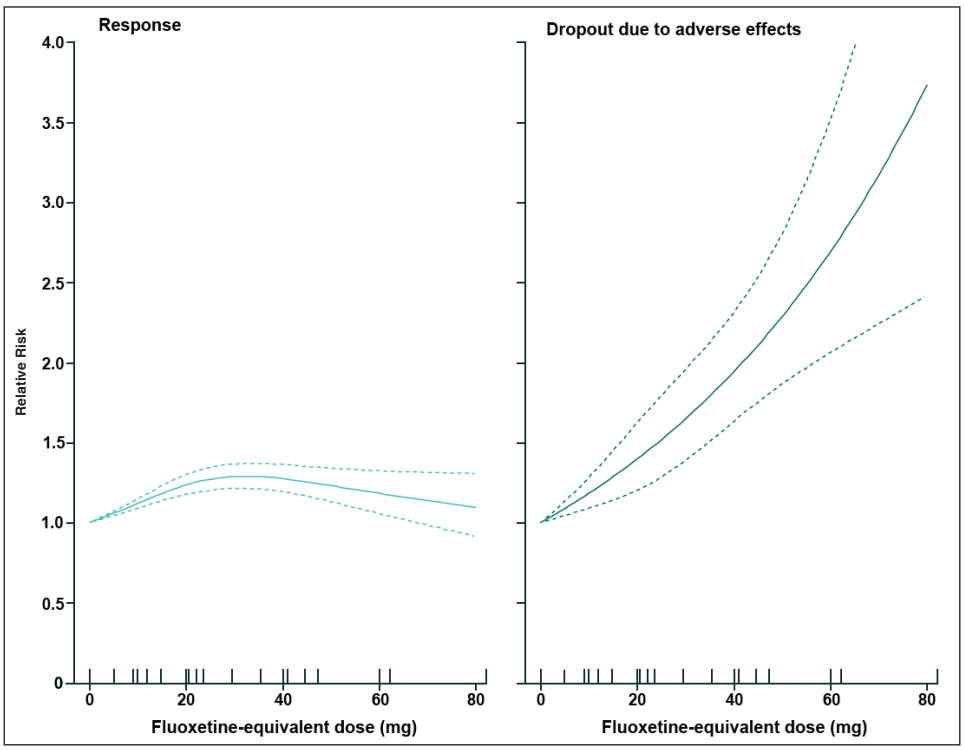
REVIEW OF: Furukawa TA et al, *Lancet Psychiatry*;2019;6(7):601–609

TYPE OF STUDY: Systematic review and meta-analysis

Most antidepressants do not have a linear response curve. In other words, the benefits level off as the dose goes up. If the dose gets too high, the side effects start to outweigh those diminishing returns. What's not clear is where the "sweet spot" lies for each antidepressant, and this study set out to capture that optimal dose range.

This dose-response meta-analysis included 77 double-blind, randomized, placebo-controlled trials of fixed-dose SSRIs (except fluvoxamine), venlafaxine, and mirtazapine in major depression (n = 19,365). Median trial length was 8 weeks (range = 4–12 weeks). Primary outcomes were efficacy (treatment response defined as 50% or greater reduction in depressive symptoms), tolerability (dropouts due to adverse effects), and acceptability (dropouts for any reason).

The best balance of efficacy, tolerability, and acceptability was achieved at low to medium doses of these antidepressants (see table). At higher doses (> 40 mg of fluoxetine equivalents), the benefits plateaued and dropouts from side effects showed steep, linear-to-exponential curves. Venlafaxine was unique in that its efficacy continued to increase up to 375 mg, though it started slowing at doses above 150 mg.



Relationship of Dose to Response and Adverse Effects for SSRIs Across 99 Treatment Groups *(Furukawa TA et al, 2019)*

ANTIDEPRESSANT	OPTIMAL DAILY DOSE
Citalopram	20–40 mg
Escitalopram	10–15 mg
Fluoxetine	20–40 mg
Mirtazapine	15–30 mg
Paroxetine	20–30 mg
Sertraline	50–100 mg
Venlafaxine	75–150 mg

TCPR'S TAKE

When a patient does not recover fully on an antidepressant, it's tempting to keep raising the dose. That strategy may work sometimes, but this study suggests that for many on second-generation antidepressants, an increased dose is more likely to cause side effects than therapeutic gains. If you go to a higher dose, measure the outcomes, and consider dropping back down if there's no clear improvement.

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

As we went to press with this antidepressant update, a new study was released that analyzed the same data by age. To learn more, listen to our 3/30/20 podcast, "Antidepressant Doses Also Vary by Age." Search for "Carlat" on your podcast store.

News of Note

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randomized, placebo-controlled trials that involved close to 2,000 subjects and lasted 1 to 12 months. One of those studies included a zolpidem (Ambien) arm. Both 5 mg and 10 mg doses of lemborexant outperformed zolpidem on subjective and objective measures of sleep initiation and maintenance. Suvorexant has also gone head-to-head with zolpidem, where it proved better at maintaining sleep but less effective at initiating it. On the surface, those results imply that suvorexant is a less powerful hypnotic, but keep in mind it went head-to-head with high-dose, instant-release zolpidem (10 mg) while lemborexant was compared to low-dose, controlled-release zolpidem (6.25 mg).

The orexin mechanism suggests a better safety profile and less addictive

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News of Note

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potential than the z-hypnotics. Based on the research on suvorexant, this class appears to lack tolerance and withdrawal effects, but may actually have an abuse potential that's similar to the z-hypnotics. Both lemborexant and suvorexant have gone through placebo-controlled trials in the elderly, and no new safety concerns were found in that vulnerable population (Herring WJ et al, *Alzheimers Dement* 2020;10.1002). Lemborexant has gone head-to-head with z-hypnotics, where it proved less likely than zolpidem to cause imbalance after middle-of-the-night awakening, and less likely to impair driving the next morning compared to the European z-hypnotic zopiclone.

TCPR'S TAKE

Orexin antagonists improve on the safety of older hypnotics, but the new addition to this class offers no clear advantage over its predecessor. It will take a year or two of post-market surveillance to get to know lemborexant better. Until then, suvorexant, which has stood the test of time since 2014, is the safer choice in this class.

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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. In studies comparing oxcarbazepine to carbamazepine for bipolar disorder, oxcarbazepine was about 20% less likely to cause side effects. However, oxcarbazepine has a higher risk of which side effect? (LO #1)

   [ ] a. Weight gain
   [ ] b. Blurred or double vision
   [ ] c. Hyponatremia
   [ ] d. Agitation

2. According to Dr. Kelly, which of the following is true about hypomania in patients with bipolar II? (LO #2)

   [ ] a. Classic, euphoric hypomania is more common than dysphoric mania in bipolar II
   [ ] b. Patients with bipolar II most often seek treatment only when they're in the midst of a classic hypomanic episode
   [ ] c. Patients with bipolar II tend to have more intense but shorter durations of hypomania compared to those with bipolar I
   [ ] d. In bipolar II, dysphoric or mixed hypomanias are more common than classic, euphoric ones

3. According to a 2019 study, the best balance of efficacy, tolerability, and acceptability of fixed-dose SSRIs was achieved at medium to high doses. (LO #3)

   [ ] a. True
   [ ] b. False

4. A 35-year-old woman with bipolar disorder is taking oxcarbazepine (1200 mg/day) to augment lithium. Which of the following medications could have a serious interaction with the oxcarbazepine? (LO #1)

   [ ] a. Prednisone
   [ ] b. Iron supplements
   [ ] c. Birth control medications
   [ ] d. Vitamin D

5. According to studies, patients with bipolar II spend approximately _____ of their lifespan in depression. (LO #2)

   [ ] a. Under 20%
   [ ] b. 35%
   [ ] c. 50%
   [ ] d. Over 65%

6. According to a 2019 meta-analysis of fixed-dose studies with SSRIs, higher doses were significantly associated with an increase in dropouts due to side effects. (LO #3)

   [ ] a. True
   [ ] b. False

Expert Interview

Continued from page 4

a fairly common disorder. Basically, I have very ill patients and I'm desperate to find something that helps them. In bipolar disorder, the worst morbidity and mortality outcomes stem from the illness, not the medications. Evidence-based medicine doesn't need to be limited to double-blind, placebo-controlled trials. As long as you're careful with the medications, it's reasonable to try things from even a case series when nothing else has worked.

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

To learn more, listen to our 3/9/20 podcast, "The Choice: Oxcarbazepine or Carbamazepine in Bipolar." Search for "Carlat" on your podcast store.

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In Brief

Sugar's Pleasures Prove Illusory. Sugar failed to boost mood in a meta-analysis of 31 randomized controlled trials that examined the acute effects of sugar ingestion in healthy adults. Instead, the subjects were more tired and less alert 1 hour after ingestion of glucose and other sugars (Mantantzis K et al, *Neurosci Biobehav Rev* 2019;101:45–67). Chronic consumption of sugar is associated with clinical depression, and that effect looks even worse with artificial sweeteners (Guo X et al, *PLoS One* 2014;9(4):e94715).

More on lifestyle, mood, and diet in this month's podcasts. This month's bonus podcasts will feature an interview with the lead investigator on the meta-analysis mentioned above ("***Research Theme Park: Sugarland,***" 3/23/20) and a guide to the "***Top Lifestyle Tips for Depression and Bipolar***" (3/16/20). Search for "Carlat" on your podcast store.

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