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Chris Aiken, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Schizophrenia

Learning Objectives

After reading these articles, you should be able to:

1. Compare lecanemab and aducanumab in terms of clinical efficacy.
2. Identify the benefits of shorter therapy sessions, trust-building, shared interests, and cautious self-disclosure in treating schizophrenia.
3. Summarize some of the current research findings on psychiatric treatment.

Lecanemab Breaks Thin Ground in Dementia

Chris Aiken, MD. Editor-in-Chief, The Carlat Psychiatry Report. *Assistant Professor, NYU Langone Department of Psychiatry. Practicing psychiatrist, Winston-Salem, NC.*

Dr. Aiken has no financial relationships with companies related to this material.

On July 5, 2023, the FDA approved lecanemab (Leqembi) in Alzheimer's dementia. The drug has been called "groundbreaking," but the ground it stands on is not very firm, with questionable efficacy, a $26,500 annual cost, and a 12.6% risk of cerebral edema.

Lecanemab vs aducanumab

In one sense, lecanemab does break new ground. It is the first amyloid-reducing medication to demonstrate clinical efficacy in dementia, something that cannot be said for aducanumab (Aduhelm), the other antiamyloid medication. While lecanemab has full FDA approval, aducanumab earned only provisional approval in 2021 under an "accelerated" pathway that allows investigational drugs to enter the market before they are fully investigated (van Dyck CH et al, *N Engl J Med* 2023;388(1):9–21). Accelerated

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Highlights From This Issue

Feature article. We look at how patient factors can personalize the selection of antidepressant augmentation.

Q&A on page 1. Mark Ruffalo brings forth a psychotherapy approach to schizophrenia.

Research update on page 6. New research on meds that cause switches into depression in bipolar disorder.

Q&A With the Expert

A Therapeutic Approach to Schizophrenia
Mark L. Ruffalo, MSW, DPsa

Editor-in-Chief, The Carlat Psychotherapy Report. *Psychotherapist in private practice in Tampa, Florida. Assistant Professor of Psychiatry at the University of Central Florida College of Medicine and Adjunct Instructor of Psychiatry at Tufts University School of Medicine.*

Dr. Ruffalo has no financial relationships with companies related to this material.

TCPR: How do you establish trust with patients who have psychosis?

Dr. Ruffalo: Shorter sessions are more appropriate for psychotherapy with schizophrenia, like 30 minutes instead of the usual 45–50 minutes. Longer sessions tend to increase the patient's interpersonal anxiety. Another tip is to allow the patient an adequate degree of freedom in the therapy space. For instance, if the patient wants to get up off the couch and walk around the room, I let them do that. If the patient wants to talk about something that doesn't, on the surface, seem all that important, I let them do that (Ruffalo ML, *Psychiat Clin Psychopharmacol* 2023;33:222–228).

TCPR: How long does it take to establish trust?

Dr. Ruffalo: It may take many weeks or months for them

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Lecanemab Breaks Thin Ground in Dementia

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approval is the result of a long struggle between the FDA and the public that began in 1988 when AIDS activists occupied the FDA headquarters demanding faster access to investigational therapies. The accelerated pathway speeds access to promising but unproven drugs, with the expectation that the bulk of the safety and efficacy data will be gathered after the launch.

Aducanumab failed in its clinical trials, but was approved because it reduced a biomarker for Alzheimer's: amyloid plaques. Medicare has refused to cover this drug, which is slotted to come off the market in 2024 due to low sales. Meanwhile, lecanemab has earned full FDA approval and comprehensive Medicare coverage.

Meaningful efficacy?

Lecanemab also reduces amyloid plaques, and like its predecessor it began with disappointing clinical results. It failed to make a difference in its first randomized trial of 856 patients (Swanson CJ et al, *Alzheimers Res Ther* 2021;13(1):80). That was followed in early 2023 by the larger Clarity trial, which is the first and only trial to show a statistically significant difference in clinical outcomes with antiamyloid therapy. In Clarity, lecanemab did not improve cognition, but it slowed the decline by 27% compared to placebo after 18 months in 1,795 patients ages 50–90 (average 71) in the early phase of Alzheimer's disease (van Dyck et al, 2023).

There are several reasons to be skeptical of these results. First, they arrived on the heels of 14 negative trials of antiamyloid drugs (Ackley SF et al, *BMJ* 2021;372:n156). Most of these were undertaken in patients who were in the early phase of Alzheimer's or had mild cognitive impairment. Second, lecanemab's positive study enrolled a highly selective population. Only 30% of those screened met the inclusion criteria, which limited the population to those with active amyloid plaques, no more than mild cognitive impairment (Mini-Mental State Exam score ≥22), no ischemic brain disease, and no active medical or psychiatric illness (Walsh S et al, *BMJ* 2022;379:o3010).

Finally, although slowing the decline by 27% sounds impressive, many believe the difference is so small that it won't be appreciated by patients or their caregivers. Researchers estimate that a 0.98–1.63 point reduction in the Clinical Dementia Rating (CDR) is needed to make a meaningful difference, but lecanemab only reduced the CDR by 0.35–0.62 relative to placebo. By comparison, donepezil (Aricept) reduced the CDR by 0.69 in Alzheimer's and is estimated to slow the rate of decline by 25%–50% per year (Rogers SL, *Dement Geriatr Cogn Disord* 1998;9 (Suppl 3):29–42).

The risk: amyloid-related imaging abnormalities

Lecanemab's ability to remove amyloid plaques is its main selling point, but this is also responsible for its main risk: cerebral edema, officially known as amyloid-related imaging abnormalities (ARIAs). These occurred in 12.6% of treated patients. Most ARIAs are asymptomatic, although intracerebral hemorrhage and death can occur. ARIAs are detectable on an MRI, which is required at baseline and approximately every three months during treatment. ARIAs are more common in carriers of the apolipoprotein E epsilon 4 (APOE-ε4) gene, and testing for this gene is required before starting lecanemab. APOE-ε4 is also a risk factor for Alzheimer's dementia.

Lecanemab's other burdens are tolerability and price. The IV infusions, which last an hour and are delivered every two weeks, can cause nausea and flu-like symptoms. Most Medicare plans will pay 80% of the $26,500 annual cost of the drug, and the out-of-pocket costs for the required scans are unclear (on average, the full price is $6,000 for the initial PET scan and $4,000–$6,000 annually for the MRIs).

Other options

Central to lecanemab's approval is the idea that it changes the course of the disease by removing amyloid plaques. However, amyloid is just one of many potential causes of Alzheimer's. Other FDA-approved options address potential mechanisms as well, like elevations of glutamate (memantine) and acetylcholine (cholinesterase inhibitors), and some even lower amyloid plaques, although to a lesser degree than lecanemab (Saeedi M and Mehranfar F, *Recent Pat Biotechnol* 2022;16(2):102–121). Tau proteins are another mechanism under investigation. Like lecanemab, none of these approved medications improve cognition.

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Lecanemab Breaks Thin Ground in Dementia

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All of them slow the progression of the disease, and there is no evidence that lecanemab brings superior safety or efficacy to the table.

Current guidelines recommend starting with a cholinesterase inhibitor in Alzheimer's dementia. All have comparable efficacy, and donepezil—which has approval in all levels of severity—is a reasonable first choice (Grossberg GT et al, *J Alzheimers Dis* 2019;67(4):1157–1171). If needed, donepezil can be augmented with memantine. The combination has FDA approval as Namzaric (generic substitution of the separate medications is acceptable, but keep in mind that Namzaric contains extended-release [XR] memantine, and 14 mg of XR memantine = 10 mg of immediate-release memantine). Compared to donepezil alone, the combination reduces cognitive decline (small effect size), improves functioning (medium effect size), and reduces psychiatric and behavioral symptoms (large effect size) (Chen R et al, *PLoS One* 2017;12(8):e0183586).

These first-line therapies are safer than lecanemab. Their main risk is tolerability. For cholinesterase inhibitors, that means dizziness, nausea, low appetite, and diarrhea. For memantine, headache, confusion, and somnolence are common.

Antipsychotics are best avoided in dementia as they raise mortality risks and interfere with the benefits of cholinesterase inhibitors. Most bring little benefit for agitation, with the exception of brexpiprazole (Rexulti), which was FDA approved for this use in 2023. The approval was based on two three-month randomized controlled trials involving 703 patients, which found efficacy at 2 mg/day but not at lower doses (Grossberg GT et al, *Am J Geriatr Psychiatry* 2020;28(4):383–400). For a quick visual, see the table "FDA-Approved Medications for Dementia."

None of these treatments have problematic interactions with lecanemab, but it is not yet clear where the IV infusion fits in the algorithm for Alzheimer's dementia.

FDA-Approved Medications for Dementia

	Medication	Indication and Dosage
Cholinesterase Inhibitors	Donepezil (Aricept)	• Mild to severe Alzheimer's • 5–23 mg/day (higher doses for severe Alzheimer's)
	Galantamine (Razadyne)	• Mild to moderate Alzheimer's • 8–24 mg/day, divided BID or as extended release (XR)
	Rivastigmine (Exelon)	• Mild to moderate Alzheimer's and mild to moderate dementia associated with Parkinson's disease • 1.5–6 mg BID with meals or as XR patch
NMDA Antagonist	Memantine (Namenda)	• Moderate to severe Alzheimer's • 5–20 mg/day, divided BID or as XR (14 mg XR = 10 mg immediate release)
Combo	Donepezil and memantine (Namzaric)	• Moderate to severe Alzheimer's • Titrate to 28 mg/10 mg QHS
Amyloid Antibody	Aducanumab (Aduhelm)	• Mild cognitive impairment or mild Alzheimer's with amyloid beta pathology confirmed by PET scan (approval was provisional and drug is due to be taken off the market in 2024) • 10 mg/kg IV Q4 week
	Lecanemab (Leqembi)	• Mild cognitive impairment or mild Alzheimer's with amyloid beta pathology confirmed by PET scan • 10 mg/kg IV Q2 week
Antipsychotic	Brexpiprazole (Rexulti)	• Agitation associated with dementia due to Alzheimer's • Titrate to 2–3 mg/day

Tacrine, a cholinesterase inhibitor, was the first drug approved for dementia and was taken off the market in 2013 due to hepatotoxicity.

CARLAT VERDICT Lecanemab's ability to reduce amyloid plaques raises hopes that it will alter the course of Alzheimer's disease, but so far, those hopes are unproven. Instead, amyloid reduction causes cerebral swelling for one in eight patients.

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Expert Interview

Continued from page 1

to feel comfortable in session, but once they are, they begin to open up about their inner world. They may tell us things they have not revealed to any other person on earth. As psychoanalyst Silvano Arieti said, "Sooner or later, the patient gives us the gift of trust." And a gift it is, indeed.

TCPR: What else improves the alliance?

Dr. Ruffalo: I look for what they are interested in. It helps to relate on a shared topic, like sports or movies. If the patient mentions a streaming show, I may not watch it, but I will at least read about it. That helps them feel that they are understood, that I care about them and am interested in the way they see things. To paraphrase Harry Stack Sullivan, the patient must feel that he is no longer alone in the world in his relations with the therapist. This also goes better in person, rather than through telehealth (Krupnik V, *Contemp Psychother* 2023;53:207–215).

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Expert Interview
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TCPR: How do you handle personal questions that patients ask?
Dr. Ruffalo: I tend to be a bit more liberal in my use of self-disclosure with schizophrenia patients. I may talk about day-to-day life, my own interests and hobbies, etc. I believe in boundaries and the therapeutic frame, but sometimes declining to answer questions can backfire because it gives the sense that you are closed off or not real. This is especially important in the early stages of treatment, where the patient needs to have that sense that you're a real person who shares in their experience of the world.
TCPR: What goals do people with schizophrenia bring to therapy?
Dr. Ruffalo: A common one is to rejoin the social fabric of life, to regain some ability to develop and maintain relationships.
TCPR: How do you help someone with minimal social skills build a social world?
Dr. Ruffalo: It takes time, but there is usually some improvement within a year. You start with more reachable goals. For instance, you might propose "Why don't you text an old friend this week? Why don't you reach out to someone on Facebook whom you'd like to talk to but haven't spoken with in a long time, perhaps since before you fell ill?" Gradually they get more comfortable in social settings, and as their relational life improves, their symptoms decrease.
TCPR: How does this lead to symptomatic improvement?
Dr. Ruffalo: Take a patient who hears critical voices telling him that he's no good, that he doesn't deserve to live, that he should kill himself. As he builds a better life, his self-esteem will improve. He might tell you "Well, you know, I was able to do voc rehab, and that helped me get a job, and now I'm meeting some people there who want to hang out outside of work." Through this, we work on his perspective of himself and gain some distance from the negative voices. If he can understand that the voices are not real but representations of his own views about himself, they become less threatening. A patient at a later stage of treatment might be able to tell you that they transform their feelings about themselves into concrete delusions and hallucinations.
TCPR: How do you build the motivation to change?
Dr. Ruffalo: I'll ask them to imagine what it would feel like if they made those changes. "How would you feel different about yourself if you got this job?" or "What would it mean to you if that person you'd like to get to know agreed to meet you for breakfast?"
TCPR: What problems do patients with schizophrenia encounter as they take on the challenges of jobs and new relationships?
Dr. Ruffalo: A common problem is that other people interpret their flat affect and other negative symptoms as disinterest, like "He doesn't smile at me. He's not laughing at my jokes, so he must not like me." Patients are often quite attuned to this problem, to the way that other people see them as different or odd. This has to be handled very delicately in psychotherapy. If we can teach and role-play some skills, if we can model for the patient some social interaction in the session, then slowly over time the patient may begin to feel a bit more comfortable in these settings and approach a more normal interaction.

"Shorter sessions are more appropriate for psychotherapy with schizophrenia, like 30 minutes instead of the usual 45–50 minutes. Longer sessions tend to increase the patient's interpersonal anxiety."

Mark L. Ruffalo, MSW, DPsa

TCPR: Do you role-play conversation skills, like asking them to tell you about a movie they saw?
Dr. Ruffalo: Yes. In my experience the practice they need often has to do with relationships, with asking someone out, with approaching someone they are interested in. They might ask "What should I say? I'd really like to ask her out." Role-playing is also helpful for job interviews and interactions with family. You can also teach social skills, basic things like eye contact—not too much, not too little; respecting personal space; smiling; give-and-take in conversation; starting and ending conversation (Turner DT et al, *Schizophr Bull* 2018;44(3):475–491). But I wouldn't jump into these skills too soon.
TCPR: What is the risk of attempting to tackle these skills too soon?
Dr. Ruffalo: Sometimes the lack of eye contact and social reciprocity makes the therapist uncomfortable, and if the therapist is unaware of their own countertransference, they might jump into social skills too soon, which can backfire. Therapists get into trouble when they go into "problem-solving" mode before there is sufficient trust in the treatment relationship. The patient has to be comfortable in the therapy room first.
TCPR: What do you tell patients about their diagnosis?
Dr. Ruffalo: When it comes to naming the disorder, actually calling it what it is, I think this is something that we ought to think about on a case-by-case basis. I think some people are very quick not just to apply a diagnosis, but to inform the patient of the diagnosis. And while in many cases this can be helpful, I think in some cases it can be detrimental and harmful, especially early on in the treatment. Now with that being said, I certainly believe in psychiatric diagnosis and I certainly believe in the concept of schizophrenia. But whether or not we should introduce that to the patient is a more delicate clinical question, and I think it warrants a little bit of care.
TCPR: Some patients get demoralized about the diagnosis. How do you work with that?
Dr. Ruffalo: When it comes to prognosis, I follow the patient's lead. Some come right out and ask "Am I going to get better?" It's important to deal with this very carefully and not overpromise things, while also not underpromising or relaying a grim outlook. Even if the prognosis is poor, we need to be supportive, to help with day-to-day problems that occur in life. Often there is some connection that can be made with the therapist, and that alone may ward off potential suicide. It is early in the course of the illness that the risk of suicide is highest.

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Expert Interview
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TCPR: How do you help people with schizophrenia manage their psychotic symptoms?

Dr. Ruffalo: One way is to teach them to adopt a "listening attitude." Just before a hallucination, patients often have a brief moment of heightened sensation where they expect the hallucination is coming on. If they can catch themselves in this momentary state, the frequency and intensity of the hallucinations will decrease (Ruffalo ML, *Psychoanal Soc Work* 2019;26:2;185–200).

TCPR: Where does that idea come from?

Dr. Ruffalo: It was developed by Silvano Arieti, a psychoanalyst who tried to bring together psychological and biological theories of schizophrenia in the 1960s and 1970s. More recently his theory was validated by Ralph Hoffman's group at Yale. Using fMRI, they found activation in the left insula just before a hallucination. This is the same part of the brain that gets activated when people—all people—hear ambiguous sounds and try to make sense of them. Those pathways seem to go awry in schizophrenia. Hoffman calls it a "prehallucination auditory expectancy" (Hoffman RE, *Schizophr Bull* 2010;36(3):440–442).

TCPR: Are you helping patients gain awareness of that moment, before it goes awry?

Dr. Ruffalo: Yes. It gives them some ability to control when and how they experience a hallucination. Of course, this doesn't hold true for every patient. For some patients this technique falls flat and doesn't work. But for others it is quite helpful.

TCPR: How do you help them gain that awareness?

Dr. Ruffalo: I ask "What is it that you felt right before you heard that voice?" They may say "There was just something that changed. I just came to expect something to happen there." Often it's a feeling of fear, of foreboding, which may be related to their paranoia.

TCPR: Once they recognize the space, what do they do?

Dr. Ruffalo: Just the act of recognizing it is enough to give them more control over the symptom and reduce the frequency of the hallucinatory experience. They gain control over what they pay attention to. Let me add caution. I'm not saying that patients are responsible for their symptoms. But there is a common theme in psychotherapy of helping patients take on a more active role in reducing those symptoms.

TCPR: Can you give an example?

Dr. Ruffalo: Here is something a patient shared about their growth (they gave permission to publish):

> *"The work didn't click for me until years in. Every psychotic experience was always preceded by a split-second shift in my emotional state. Over time, I was able to feel this window open up, and my experiences slowly dissipated. I still experience psychotic symptoms but at a much less frequent rate. Every session, a new layer of what has happened to me has unraveled through therapy. Almost every time a link has been discovered, I subsequently experience fewer symptoms."*

TCPR: Any tips on working with patients' families?

Dr. Ruffalo: One thing I emphasize for families is to do whatever they can to minimize the degree of anxiety in the household. This relates to research going back to the 1960s where they found that higher levels of *expressed emotion* in the home increase the risk of relapse in schizophrenia. *(Editor's note: The three types of expressed emotion are described in the table "Expressed Emotions in Families With Schizophrenia": critical comments, hostility, and emotional overinvolvement, along with two that reduce relapse rates: warmth and positive comments.)* Families with high levels of expressed emotion are two to four times more likely to experience relapse, and in controlled trials those relapse rates go down when we help families reduce those heated interactions (Ma CF et al, *Psychol Med* 2021;51(3):365–375).

TCPR: So the idea is to help families recognize and reduce those types of emotional expression?

Dr. Ruffalo: Yes. Families need to lower their demands, reduce conflict, avoid sensory overstimulation, and allow the patient to have their own space and to operate with reasonable freedom in their day-to-day life. By "reasonable" I mean with some constraints to avoid serious harm (Kavanagh DJ, *Br J Psychiatry* 1992;160:601–620).

TCPR: What books do you recommend for families?

Dr. Ruffalo: *Surviving Schizophrenia* by E. Fuller Torrey is a good one (Harper; 2019). It offers strategies for day-to-day affairs when a family member has active psychosis. Silvano Arieti also wrote a family guide titled *Understanding and Helping the Schizophrenic: A Guide for Families* that takes a more psychological approach. The National Alliance for the Mentally Ill (NAMI) also offers courses for families in many communities.

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

Expressed Emotions in Families With Schizophrenia

Interactions to Decrease	
Critical comments	Statements that express disapproval, resentment, or rejection or that are delivered in a critical voice.
Hostility	An overarching attitude that blames the patient for the symptoms of their disorder. The patient becomes the scapegoat for all the problems in the family.
Emotional overinvolvement	The family takes over the patient's life in an effort to protect them. Family members respond with intense hope or disappointment upon any change in symptoms. The self-sacrificing behaviors cause the patient to feel guilty, eroding their already fragile sense of boundaries and autonomy.
Interactions to Increase	
Warmth	Showing empathy, kindness, and compassion, often through body language and tone of voice.
Positive comments	Specific comments that show appreciation for the patient, acknowledge the progress they've made, or express optimism about their illness.

Research Updates IN PSYCHIATRY

MOOD DISORDERS

Mood Switching in Bipolar Disorder

Jesse Koskey, MD. Dr. Koskey has no financial relationships with companies related to this material.

REVIEW OF: Barbuti M et al, *Eur Neuropsychopharmacol* 2023;73:1–15

STUDY TYPE: Systematic review

Some medications are associated with treatment-emergent mania, but less is known about treatment-emergent depression. This analysis looked at switches in both directions. The authors excluded randomized controlled trials and looked only at observational studies, arguing that doing so would better capture the real-world situations our patients face.

The study included a gamut of 10 prospective and 22 retrospective studies ranging from 1982 to 2020. Each study included 30–3,000 patients with bipolar I or bipolar II disorder from a mix of outpatient and hospital settings. Almost all examined treatment-emergent mania or hypomania (collectively, TEM), and 11 included mixed mood episodes. There were only three studies of treatment-emergent depression (TED). Because of this heterogeneity, the reviewers didn't quantify their findings, but summarized them qualitatively.

Across the studies, TEM occurred between 17% and 49% of the time. TEM was 7.4 times more likely when antidepressants were involved—especially tricyclics and antidepressant monotherapy. Bupropion was the antidepressant least associated with TEM. In contrast to other reports, bipolar II was more associated with TEM than bipolar I. Hypomania came on more rapidly than mania after starting an antidepressant. Other risk factors for TEM included prior episodes of TEM, history of hospitalizations, rapid cycling, continuous mood episodes, female sex, substance use, younger age of onset, and bipolar disorder that first presented as depression. Atypical antipsychotics and mood stabilizers, particularly lithium, were protective against TEM.

TED was reported 5%–16% of the time in patients with bipolar I disorder (there were no data about TED in bipolar II). First-generation antipsychotics, either as monotherapy or in combination with atypicals, were associated with TED. Other risk factors included more severe mood symptoms, a higher number of prior depressions, more depressions than manias, depressive temperament, and substance use.

While observational data show us what to expect in real-world practice, they tell us nothing about causation. However, controlled trials suggest a causal relationship between first-generation antipsychotics and TED, particularly with haloperidol and perphenazine (Goikolea JM et al, *J Affect Disord* 2013;144(3):191–198; Zarate CA and Tohen M, *Am J Psychiatry* 2004;161(1):169–171).

CARLAT TAKE

Switches into mania are common with antidepressants, particularly if they are tricyclics or used as monotherapy. Switches into depression are more common when first-generation antipsychotics are used to treat mania.

DEPRESSION

Ketamine Fails to Outperform Placebo for Depression in Patients Under Anesthesia

Awais Aftab, MD. Dr. Aftab has no financial relationships with companies related to this material.

REVIEW OF: Lii TR et al, *Nat Mental Health* 2023;1:876–886 [Epub ahead of print]

STUDY TYPE: Randomized triple-blind placebo-controlled trial

Ketamine has rapid and robust antidepressant effects. However, critics have pointed out that ketamine's dissociative effects may make subjects in clinical trials aware that they have received the active drug, breaking the blind and inflating the treatment's efficacy. Supporting that is the fact that ketamine's efficacy has been higher in trials that compared it to an inert placebo than those that compared it to a psychoactive substance like a benzodiazepine (Wilkinson ST et al, *Neuropsychopharmacology* 2019;44(7):1233–1238). This new study sought to eliminate those expectancy effects by administering ketamine under general anesthesia.

The authors randomized 40 patients with moderate to severe major depressive disorder who were undergoing elective surgery to receive either a single infusion of ketamine (0.5 mg/kg, the usual dose for treatment-resistant depression) or saline placebo. Both were given while patients were under anesthesia for routine surgeries. The primary outcome was depression severity measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) at one, two, and three days post-infusion. Clinical response, defined as a 50% or greater reduction in MADRS scores from screening baseline, was a secondary outcome. Subjects were followed for 14 days after infusion. The study was funded by a grant from the Society for Neuroscience in Anesthesiology and Critical Care.

Surprisingly, no significant difference emerged between ketamine and placebo groups in the three-day follow-up. Sixty percent of patients in the ketamine group, vs 50% in the placebo group, had a clinical response on day one, and 45% vs 50% had a clinical response on day three.

In this study, ketamine's antidepressant effect was similar to previous reports, but the placebo effect was unexpectedly high, leading to no significant difference between the two. Group assignment didn't influence depression outcomes. Two subjects in the ketamine group and one in the placebo group received nitrous oxide, while standard general anesthesia was maintained with propofol and isoflurane. Less than half of the subjects correctly identified their treatment, with similar distribution in both groups. Interestingly, those who believed they received ketamine improved more, regardless of their actual treatment, hinting at the influence of expectancy. It's possible that conscious experience of ketamine's psychoactive effects plays a role in improving depression,

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CME Post-Test

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1. Which statement best describes the clinical efficacy of lecanemab versus aducanumab in Alzheimer's dementia (LO #1)?
   - [ ] a. Lecanemab demonstrated statistically significant improvements in cognitive function compared with aducanumab
   - [ ] b. Lecanemab showed worse clinical efficacy compared with aducanumab
   - [ ] c. Lecanemab showed clinical efficacy across multiple trials, while aducanumab did not
   - [ ] d. Lecanemab slowed the decline in cognitive function, while aducanumab failed to show any clinical benefit

2. What distinguishes lecanemab from aducanumab in terms of Medicare coverage (LO #1)?
   - [ ] a. Lecanemab did not receive comprehensive Medicare coverage, while aducanumab did
   - [ ] b. Lecanemab is eligible for Medicare coverage only if patients are enrolled in an NIH-sponsored clinical trial, unlike aducanumab
   - [ ] c. Both lecanemab and aducanumab have comprehensive Medicare coverage
   - [ ] d. Lecanemab is fully approved with comprehensive Medicare coverage, while aducanumab has Medicare limits

3. Which antidepressant has the lowest association with treatment-emergent mania (LO #3)?
   - [ ] a. Bupropion [ ] b. Nortriptyline [ ] c. Imipramine [ ] d. Sertraline

4. What distinguishes lecanemab from aducanumab in terms of FDA approval (LO #1)?
   - [ ] a. Lecanemab received traditional approval, while aducanumab received provisional approval
   - [ ] b. Lecanemab underwent an accelerated approval process, whereas aducanumab followed traditional approval pathways
   - [ ] c. Both lecanemab and aducanumab were fully approved by the FDA without any provisional status
   - [ ] d. Both lecanemab and aducanumab earned comprehensive Medicare coverage

5. Which best identifies a benefit of shorter therapy sessions for patients with psychosis (LO #2)?
   - [ ] a. Shorter sessions encourage patients with psychosis to focus on behavioral change
   - [ ] b. Shorter sessions decrease the likelihood of patients experiencing symptom exacerbation
   - [ ] c. Shorter sessions lessen patients' interpersonal anxiety
   - [ ] d. Shorter sessions help patients stay grounded in reality

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and that if the subjects had been awake, the ketamine group would have shown a higher response than placebo.

CARLAT TAKE

This study does not negate ketamine's antidepressant effects but reminds us how potent the placebo is in psychiatry. It's something to keep in mind as other psychoactive substances like cannabidiol and psilocybin test the limits of our blinds.

NEGATIVE SYMPTOMS

Sertraline in Schizophrenia

Richard Moldawsky, MD. Dr. Moldawsky has no financial relationships with companies related to this material.

REVIEW OF: Lang X et al, *J Transl Med* 2023(1),21:432

STUDY TYPE: Randomized controlled open-label study

Antipsychotics clearly work well for positive symptoms in schizophrenia, but they are less effective for negative symptoms. This study from China tested whether adding a selective serotonin reuptake inhibitor (SSRI) could improve negative symptoms and allow lower dosing of an antipsychotic in schizophrenia.

The study enrolled 230 treatment-naive patients who were within the first five years of a schizophrenia diagnosis. All patients were between 18 and 45 years old. Substance use disorders and significant medical problems were exclusions. Over 24 weeks, patients were randomized to receive either (a) risperidone 2–3.5 mg/day with sertraline 50–100 mg/day or (b) risperidone 4–6 mg/day alone. Clonazepam was permitted for insomnia and anxiety.

The main outcome measure was change in the Positive and Negative Syndrome Scale (PANSS), supplemented by the Hamilton Depression Rating Scale (HAM-D), the Personal and Social Performance Scale (PSP), and a side effects scale. Blind raters assessed the patients with these scales at baseline and after months one, two, three, and six. Prolactin levels were also measured. At baseline, the subjects were markedly to severely impaired.

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Over the course of the study, the risperidone-sertraline group showed more improvement than the risperidone-alone group. With more time, these differences grew, but both groups benefited from treatment. PANSS, HAM-D, and PSP scores were all superior with the sertraline combination ($p<0.03$ or better), indicating functional and symptomatic improvement. Side effects and prolactin levels were also lower in the combined-treatment group.

The dropout rate was 14%, with more dropouts in the risperidone-only group (26 patients) than the combination group (six patients). Most dropouts were due to side effects.

Unfortunately, the study design makes it impossible to tell whether the superior outcomes were due to the lower risperidone dosage or the addition of sertraline in the combination group. Also, it is possible that the observed benefits were due to treatment of an undiagnosed depressive episode, as the average baseline HAM-D score was an elevated 24.

CARLAT TAKE

Although imperfect in design, this study builds on prior evidence that SSRIs improve negative symptoms in schizophrenia. In choosing an SSRI, note that sertraline, citalopram, and escitalopram rarely cause drug interactions, whereas fluoxetine, paroxetine, fluvoxamine, and high-dose sertraline (above 150 mg) raise serum levels of many antipsychotics.

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