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Chris Aiken, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Inflammation and Depression

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

1. Identify the benefits and drawbacks of Nuedexta in dementia.
2. Discuss the correlation between inflammation and depression.
3. Summarize some of the current research on psychiatric treatment.

Nuedexta in Agitated Dementia

Treating agitation in dementia is no easy task. Behavioral interventions are first line, but they are difficult to implement and often insufficient. Psychotropics show modest benefits, but they are prone to causing adverse events. Benzodiazepines can precipitate falls, disinhibition, and confusion. Antipsychotics have a black box warning about an increased risk of death in older patients with dementia. Nuedexta recently stepped into this arena and, in doing so, created a controversy that threatens to cloud the science. In this article, I'll clarify its role in dementia with agitation.

Highlights From This Issue

Inflammation contributes to treatment resistance in depression and can be measured with a blood test, C-reactive protein (CRP).

An elevated CRP predicts a favorable response to certain antidepressants, as well as specific lifestyle interventions.

Nuedexta's expanded use in dementia is based on questionable efficacy, but it is safer than many of the psychotropics routinely used in that population. It's expensive, but there are ways to prescribe a generic equivalent.

A medicine for pseudobulbar affect

Nuedexta is approved for pseudobulbar affect (PBA). This is a syndrome of sudden, uncontrollable laughing or crying that bears no relationship to the patient's emotional state or social context or is far out of proportion to it. PBA is not a psychiatric disorder. It is caused by neurologic illnesses that disrupt the pathways

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Q&A With the Expert

Inflammatory Biomarkers in Depression
Andrew H. Miller, MD

William P. Timmie Professor of Psychiatry and Behavioral Sciences, Emory University, GA

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

TCPR: What is inflammation?
Dr. Miller: Inflammation is the body's natural response to infection or wounding. It's important for survival, but if it goes on too long it damages the body in various ways. It contributes to heart disease, cancer, metabolic disorders, and neurodegenerative disorders. Ultimately, it can change set points in the brain that influence behavior.
TCPR: Is depression an inflammatory illness?
Dr. Miller: The simple answer is no. About 30% of patients with major depression have elevated inflammatory markers, so it's a minority of patients we are talking about. The rate is higher in treatment-resistant depression, where nearly half have inflammation. There are other groups where you'll see more inflammation, like patients with obesity, significant stress, and chronic medical illnesses (*Ed note:* See "Risk Factors for Inflammation" table on page 3).
TCPR: How do you confirm inflammation once it's suspected?
Dr. Miller: The most widely accepted standard is the

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Nuedexta in Agitated Dementia
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involved in emotional regulation, such as the corticobulbar tracts and basal ganglia.

Inside Nuedexta

Nuedexta is a combination of two older medications: dextromethorphan and quinidine. Dextromethorphan is an over-the-counter cough suppressant that's usually kept behind the counter because of its abuse potential. Doses between 100 and 600 mg can cause mild stimulation and euphoria, while doses above 500 mg can cause dissociative !!hallucinations (hence the abuse potential). Quinidine is generally used for arrhythmias but is included in this formulation to harness a drug interaction. As a potent inhibitor of CYP2D6, quinidine inhibits the enzymatic breakdown of dextromethorphan, thereby raising its serum level and extending its duration.

Dextromethorphan has psychoactive effects and is being explored for a number of psychiatric conditions, including opioid withdrawal, depression, negative symptoms of schizophrenia, and agitation associated with dementia. In addition to inhibiting the serotonin and norepinephrine transporters, dextromethorphan has unique properties. It is a sigma-1 agonist and noncompetitive antagonist of the NMDA glutamate receptor (Werling LL et al, *Neurologist* 2007;13(5):272–293).

Expansion into dementia

PBA is a syndrome that nearly always occurs as part of a neurologic disorder. When it was released in 2010, Nuedexta was indicated only in PBA due to multiple sclerosis or amyotrophic lateral sclerosis (ALS). Those were, and remain, the only conditions where Nuedexta has controlled evidence for PBA.

In 2015, the FDA allowed Nuedexta to broaden its indication to PBA as a whole, regardless of the cause. The drug had by that time shown benefits in a large but uncontrolled trial of PBA due to stroke, traumatic brain injury, and dementia (Hammond FM et al, *BMC Neurol* 2016;16:89). It's with this last disorder that the use of Nuedexta started to expand.

Agitation is not part of PBA, but it's a common feature of dementia that seemed to improve along with the PBA when Nuedexta was used in dementia. That led the manufacturer, Avanir Pharmaceuticals, to sponsor a 10-week randomized, placebo-controlled trial of dextromethorphan-quinidine in patients with presumed Alzheimer's dementia and "clinically significant agitation" (Cummings JL et al, *JAMA* 2015;314(12):1242–1254). Trial participants showed modest reductions in both agitation and aggression.

With this evidence in hand, the company started encouraging physicians in long-term care facilities to use dextromethorphan-quinidine off-label for patients with dementia. But it didn't stop there: Avanir also gave kickbacks in the form of money, travel, and food to physicians who prescribed Nuedexta (www.justice.gov/news, 9/26/2019).

While questionable, Avanir's efforts paid off; prescriptions soared. A recent analysis of over 12,000 Nuedexta prescriptions found that over 50% were written for dementia and Parkinson's disease (Fralick M et al, *JAMA Intern Med* 2019;179(2):224–230). The Department of Justice got wind of this, and in September 2019, Avanir agreed to pay over $108 million in fines. This story has soured Nuedexta's reputation in dementia, but there might be something worth salvaging from this medication.

The evidence in agitation

When it comes to Nuedexta's clinical evidence in dementia with agitation, the results are mixed. So far there have been three randomized, multicenter, double-blind, placebo-controlled trials, of which two were positive and one—the largest—was negative.

The first trial used a formulation of Nuedexta with slightly more dextromethorphan than what's used for PBA (30 mg vs 20 mg). It found a small but significant reduction in the primary outcome: a single domain (Agitation/Aggression) of the Neuropsychiatric Inventory. The other trials are more difficult to interpret because they added deuterium, an isotope of hydrogen that, like quinidine, reduces the metabolism of dextromethorphan. These studies are unpublished, so we only know the bottom line. One trial used two dosages of the deuterium-Nuedexta formulation, with positive results in only one dosage. The other trial was negative (see "Clinical Trials of Nuedexta in Dementia With Agitation" table on page 3).

Risks

Dextromethorphan-quinidine (DM-Q) is generally well tolerated with a low occurrence of adverse events. In the published dementia trial, serious adverse events were falls (8.6% DM-Q, 3.9% placebo), diarrhea (5.9% DM-Q, 3.1% placebo),

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Nuedexta in Agitated Dementia

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urinary tract infections (5.3% DM-Q, 3.9% placebo), and dizziness (4.6% DM-Q, 2.4% placebo). QTc prolongation and drug interactions are additional concerns. Dextromethorphan can precipitate serotonin syndrome when combined with antidepressants, and quinidine is a potent CYP2D6 inhibitor that can raise the levels of many antidementia agents, antidepressants, antipsychotics, amphetamines, opioids, and antihypertensives.

Generic jerry-rig

Nuedexta costs around $1,235 a month, making it an expensive choice. Ostensibly we should be able to purchase generic versions of dextromethorphan and quinidine, and dose the combination appropriately, but this is difficult as the 10 mg dosage of quinidine is no longer available. Fortunately, compounding pharmacies have sprung up around the country that have no problem creating a capsule or tablet containing dextromethorphan and/or quinidine. The one caveat is this: The FDA prohibits compounding a patented formulation. The workaround is to prescribe the quinidine as a compounded medicine and the dextromethorphan separately as a liquid prescription:

- Quinidine compounded suspension, 10 mg po qd
- Dextromethorphan ER 30 mg/5 mL, take 7.5 mL po qd

Alternatively, you can slightly alter the dose of one of the medications—for example, 30 mg dextromethorphan with 10 mg quinidine. There is no need to include deuterium. I spoke with two local compounding pharmacies, and they thought the cost would be between $45 and $80 a month.

Clinical Trials of Nuedexta in Dementia With Agitation

Year	Dosage	Design	Outcome
2015	30 mg qd dextromethorphan with 10 mg bid quinidine	RCT, n = 220, 10 weeks	Positive
2019	Dose unknown, used with deuterium	RCT with 2 treatment arms, n = 410, 12 weeks	One arm was positive
2019	Dose unknown, used with deuterium	RCT, n = 522, 12 weeks	Negative

Other options for agitation

Nuedexta may not have definite proof of its benefits, but it is safer than the antipsychotics and benzos. In terms of efficacy, all of these options are questionable. Recent meta-analyses of agitation in dementia found a small effect size for antipsychotics and no benefit for benzodiazepines. Nuedexta's effect size was medium in those analyses, but they only included the positive study (Watt JA et al, *Ann Intern Med* 2019;171(9):633–642; Tampi RR et al, *Am J Alzheimers Dis* 2014;29(7):565–574).

Another path to consider is the SSRIs. There are two randomized, placebo-controlled trials of SSRIs for behavioral symptoms of dementia, and both are positive, albeit with modest benefits. One involved sertraline (50–200 mg qd), the other citalopram (30 mg qd) (Seitz DP et al, *Cochrane Database Syst Rev* 2011;CD003154). Sertraline was the better tolerated of the two. Citalopram caused a mild worsening of cognition and prolonged the QTc interval by 18 milliseconds on average.

Non-pharmacologic options exist that are safer than medications and outperformed pharmacologic treatments in a meta-analysis of agitation in dementia (Watt JA et al, *Ann Intern Med* 2019;171(9):633–642). These include music therapy, structured activity, outdoor activity, a safe place to walk, massage, touch therapy, empathic communication skills, and offering the patient simple choices.

TCPR VERDICT: Non-pharmaceutical options are first line for agitation in dementia. If medication is going to be used, sertraline is a good first choice. Nuedexta, or the generic form dextromethorphan-quinidine, is a reasonable second choice and probably safer than an antipsychotic.

To learn more, listen to our 2/17/20 podcast, "Agitation in Dementia: When the Best Medicine Is Not a Medication." Search for "Carlat" on your podcast store.

Expert Interview

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Risk Factors for Inflammation

Early childhood trauma
Recent significant stress
Treatment-resistant depression
Comorbid anxiety or neuroticism
Chronic medical illness
Obesity (BMI ≥ 30)
Recent chemotherapy or radiation
Recent bodily injury or surgery

Source: Ferrucci L and Fabbri E, *Nat Rev Cardiol* 2018:15(9):505–522; Majd M et al, *Front Neuroendocrinol* 2019:100800

C-reactive protein, or CRP. This is a protein that is produced by the liver in inflammatory states. The American Heart Association and the Centers for Disease Control and Prevention consider a CRP greater than 3 mg/L to be a marker of high inflammation. This is a low-cost lab that's usually ordered to predict the risk of heart disease. In psychiatry, you need to order it as a high-sensitivity CRP because the regular-sensitivity CRP generally does not pick up the lower levels below 3 that can inform practice.

TCPR: Does CRP have a different cutoff for inflammation in psychiatry?

Dr. Miller: We don't have a universally accepted cutoff in psychiatry. Some studies have used 1 mg/L. For example, a CRP above 1 mg/L predicts a more favorable response to bupropion than to an SSRI. Inflammation is on a spectrum, and the higher the CRP is, the more inflamed the patient tends to be (Jha MK et al, *Psychoneuroendocrinology* 2017;78:105–113). For the purposes of this interview, I'll use a cutoff of 3 mg/L when referring to "inflammation."

TCPR: Is CRP ready for prime time in psychiatry?

Dr. Miller: I believe it is. There are other markers of inflammation,

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like interleukin-6 (IL6), but these tests are not as stable as CRP. They tend to fluctuate with circadian rhythms and acute stress, including the stress of a venous puncture when blood is drawn. CRP has a long half-life, so it stays more constant and is not as vulnerable to those perturbations.

TCPR: What can cause a false positive with CRP?

Dr. Miller: False positives are rare, but I'd consider them if your patient has a high CRP but no clear reason to be inflamed. Sometimes we see a false positive from an acute infection, like an upper respiratory infection, or from seasonal allergies. When you suspect something like that, I would repeat the test later.

TCPR: How do patients with inflammation look in the office? Are their symptoms any different from patients with non-inflammatory depression?

Dr. Miller: Based on what we know about the impact of inflammation on neurotransmitter systems and neurocircuits that regulate motivation and motor activity as well as anxiety and alarm, the typical patient with high inflammation would be expected to have anhedonia and low motivation (Miller AH and Raison CL, *Nat Rev Immunol* 2016;16(1):22–34). There's a global lack of pleasure and enjoyment. They may also have prominent anxiety, fatigue, and psychomotor retardation. Although these symptoms are seen in many depressed patients, their occurrence in combination with an elevated CRP would raise the suspicion that they may stem from inflammation.

TCPR: What about aging? Is that an inflammatory process?

Dr. Miller: Yes, and there's even a word for it: "inflammaging." Inflammation accelerates aging, both in the body and the brain, which can make patients look older than their stated age. We tend to see lower levels of CRP in adolescents with depression, but inflammation can happen at any age.

TCPR: Some of the psychiatric studies on inflammation have focused on obesity. Why is that?

Dr. Miller: Obesity also has a very high overlap with inflammation. Fat cells grow quickly and outstrip their blood supply, which causes those cells to die. Inflammation is a response to injury and cell death. Also, the Western diet—fast food, fried food, processed and sugary foods—contributes to inflammation through various mechanisms, such as increased intestinal permeability, which is also called leaky gut.

"About 30% of patients with major depression have elevated inflammatory markers. The rate is higher in treatment-resistant depression, where nearly half have inflammation."

Andrew H. Miller, MD

TCPR: What is leaky gut?

Dr. Miller: Leaky gut means that microbial products have penetrated from the gut into the circulation. Once in the bloodstream, they trigger immune cells to produce inflammatory cytokines. One way to prevent leaky gut is through diet, like the Mediterranean-style diet. A healthy diet is rich in fiber, which gives the gut bacteria something to chew on. If there isn't enough fiber in the diet, they will eat away at the gut lining, causing it to get thin and leak into the circulation. Diets high in sugar or saturated fats can also disrupt the gut microbiome in ways that lead to leaky gut, as can heavy alcohol use. We see this syndrome of leaky gut more often in Crohn's disease, inflammatory bowel disease, and ulcerative colitis, and it can also be a pathway to depression.

TCPR: Patients often report higher levels of depression in the months after a surgery. Can inflammation explain that?

Dr. Miller: Yes. Patients often attribute those changes to the anesthetic agents they've received, which makes sense because they are psychoactive drugs. However, inflammation both during and after surgery is associated with mood and cognitive problems.

TCPR: What do we do when we see a patient with depression, inflammation, and an elevated CRP?

Dr. Miller: There are a handful of randomized controlled trials that can guide us. An elevated CRP predicts a better response to dopaminergic or norepinephrine agents and a poorer response to SSRIs. The first study that looked at this compared nortriptyline to escitalopram (Lexapro) in 241 patients with depression. The patients with a high CRP > 3 mg/L did better on nortriptyline, while those with a low CRP below 1 mg/L did better on the escitalopram (Uher R et al, *Am J Psychiatry* 2014;171(12):1278–1286). More recently we have the CO-MED trial, which looked at bupropion augmentation of an SSRI (escitalopram) in 106 patients with major depression. When the results were first

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Treatments to Consider During Inflammation

Medications	
Bupropion	Augmentation of escitalopram with bupropion worked better in patients with an elevated CRP > 1 or obesity (BMI ≥ 30)
Nortriptyline	Patients with a CRP > 3 responded better to nortriptyline than escitalopram
Lurasidone	In a placebo-controlled trial of bipolar I depression, lurasidone's benefits increased as the CRP rose above 2
Pramipexole	Evidence for a preferential response during inflammation is suggested by animal models
Complementary and Alternative Therapies	
N-acetylcysteine (NAC)	CRP > 3 predicted response to NAC 2000 mg qd in anxiety and depression
L-methylfolate	Inflammatory biomarkers, including BMI > 30 and CRP > 5, predicted response to L-methylfolate 15 mg qd as antidepressant augmentation
Omega-3	CRP > 3 predicted response to omega-3 EPA 1060 mg/day in depression
Lifestyle	Exercise, yoga, tai chi, the Mediterranean diet, mindfulness, and CBT for insomnia all have anti-inflammatory and antidepressant effects

Expert Interview

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published in 2011, bupropion augmentation worked no better than a placebo. Later, the researchers parsed out the data by inflammatory markers. It turned out bupropion worked in the subset of patients with a mildly elevated CRP (> 1 mg/L), while the SSRI monotherapy worked better when the CRP was low (Jha MK et al, *Psychoneuroendocrinology* 2017;78:105–113).

TCPR: Why do dopaminergic medications work better during inflammation?

Dr. Miller: Based on our preclinical data, it makes sense that we'd see these results with a dopaminergic medication like bupropion. Inflammation has a profound effect on the availability of dopamine in the CNS. That's why these patients have such marked anhedonia; their reward pathways are turned down. Dopamine is where I would go first in a patient with inflammation, and that might include bupropion, pramipexole, or even L-dopa. Pramipexole works in treatment-resistant depression, and L-dopa has small studies in depression and treats psychomotor slowing, which is something we see during inflammation (Gauthier C et al, *Clin Neuropharmacol* 2017;40(6):264–267; Rutherford BR et al, *Biol Psychiatry* 2019;86(3):221–229). The pramipexole and L-dopa studies did not measure inflammatory biomarkers, but in the case of L-dopa we have animal studies that show an association (*Ed note:* See "Treatments to Consider During Inflammation" table on page 4. For more on pramipexole, see the "How to Use Pramipexole" sidebar).

TCPR: Why are serotoninergic medications less effective during inflammation?

Dr. Miller: Inflammation activates the serotonin transporter, increasing both its expression and its function. The result is that serotonin is cleared more rapidly from the synapse. SSRIs target that transporter, and it's harder for them to make an impact when there is a greater volume and number of those transporters. So we have two studies showing that escitalopram does not work as well in depressed patients with inflammation, but the data are by no means definitive.

TCPR: Last year a meta-analysis identified about a dozen anti-inflammatory treatments that work in depression. Would you use these in inflammatory states?

Dr. Miller: That we don't know, because most of those studies did not measure inflammatory biomarkers, and sometimes when they have, the expected correlation did not appear (Savitz JB et al, *Transl Psychiatry* 2018;8(1):27). So we don't really know how anti-inflammatories like minocycline and the COX-2 inhibitors are working. We do have some evidence, though, that omega-3s and L-methylfolate work better when inflammatory biomarkers are elevated. L-methylfolate is an essential cofactor in the production of dopamine, and inflammation hinders that particular pathway, so there's reason to think that L-methylfolate would be especially useful in the context of inflammation (Shelton RC et al, *J Clin Psychiatry* 2016;76(12):1635–1641; Rapaport MH et al, *Mol Psychiatry* 2016;21(1):71–79).

TCPR: What lifestyle advice would you give to a patient with inflammation?

Dr. Miller: Weight loss, diet, and exercise are particularly important. Shifting to a Mediterranean diet is associated with lower rates of depression and lower inflammatory biomarkers. Other ideas to consider are meditation, yoga,

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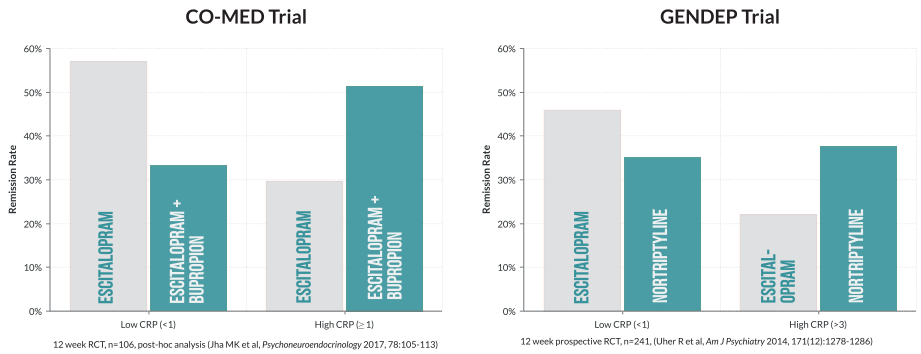
Elevated CRP Predicts Response to Bupropion and Notriptyline in MDD



How to Use Pramipexole

Pramipexole is a selective agonist at the dopamine D3 receptor, which is thought to regulate hedonic drive. It is FDA approved in Parkinson's disease and restless legs syndrome, and has five randomized controlled trials in depression. In unipolar depression it worked as monotherapy or augmentation, and in bipolar depression it worked as augmentation of a mood stabilizer (Gauthier C et al, *Clin Neuropharmacol* 2017;40(6):264–267).

Pramipexole's most common side effects are nausea, hypotension, and fatigue, which are reduced by titrating it slowly and giving the dose at night. Start with 0.125–0.25 mg qhs and raise by 0.25 mg every 5–7 days toward a target dose of 0.75–2 mg qhs. Pramipexole has a low risk of weight gain and sexual dysfunction.

Serious side effects are pathological gambling, hallucinations, and daytime somnolence. Pathological gambling is part of a spectrum of hedonic behaviors called hedonistic homeostatic dysregulation (HDD) that can include excessive masturbation, overspending on eBay, and gambling into severe debt. Aripiprazole, another D3 agonist, can also cause these problems. HDD usually occurs without manic symptoms, and it is more common when dopaminergics are used in Parkinson's disease than when they are used in mood disorders (Cartoon J & Ramalingam J, *Australas Psychiatry* 2019;27(5):456–461).

Long-term pramipexole use has been associated with congestive heart failure, but that association did not hold up in controlled investigations. Early reports of melanoma on pramipexole have since been linked to Parkinson's disease itself rather than the medication, and warnings of melanoma were removed from the prescribing information in 2018.

Research Updates IN PSYCHIATRY

SCHIZOPHRENIA

Polypharmacy in Schizophrenia

REVIEW OF: Tiihonen J et al, *JAMA Psychiatry* 2019;76(5):499–507 and Stroup T et al, *JAMA Psychiatry* 2019;76(5):508–515

TYPE OF STUDY: Retrospective non-randomized controlled trials

Antipsychotic polypharmacy is discouraged in guidelines but common in practice. Up to 30% of patients with schizophrenia are prescribed multiple antipsychotics, and combinations of antipsychotics with other drug classes are even more common. Research on these practices is sparse. Two recent studies, both large retrospective non-randomized controlled trials, attempted to clarify whether polypharmacy brings greater benefits in schizophrenia, or just greater risks.

The first study collected data from a population-wide registry in Finland on 62,250 patients with schizophrenia who were hospitalized and followed between 1996 and 2015 (median age 46; male to female ratio equal).

Hazard ratios were calculated by comparing patients on one, multiple, or no antipsychotics. Within-individual analysis was used to eliminate selection bias (ie, patients were their own controls). Of the total cohort, 67% used antipsychotic polypharmacy at some point. To exclude switches between antipsychotics, data from the first 90 days of multiple antipsychotic use were censored. The primary outcome was psychiatric rehospitalization, and secondary outcomes were mortality and medical hospitalization.

The risk of psychiatric rehospitalization was 13% lower with polypharmacy than monotherapy (HR 0.87; CI 0.85–0.88). That risk was lowest with the combination of clozapine and aripiprazole: 58% lower than no antipsychotic use (HR 0.42; CI 0.39–0.46) and 14% lower than clozapine alone (HR 0.86; CI 0.79–0.94). Among the top 10 treatments with the lowest risk of rehospitalization, only one was monotherapy: clozapine. Remarkably, polypharmacy was also associated with a lower risk of hospitalization due to medical illness and mortality.

The second study evaluated the effects of adding different drug classes to standard treatment in schizophrenia. Using a Medicaid registry, 81,921 patients with schizophrenia on antipsychotic therapy were followed for one year after starting an additional psychotropic (mean age 41; 54% male). Patients who were already on multiple psychiatric medications or who filled their antipsychotic inconsistently were excluded from the sample (n = 241 and 579).

Hazard ratios were calculated by comparing patients based on whether they were prescribed antidepressants, benzodiazepines, or mood stabilizers vs additional antipsychotics. Patients in each of the treatment groups were demographically similar. Those who did not start a new psychotropic were not included in the comparisons, as it was thought they represented a group with fewer comorbidities and better prognosis. Dropouts were handled by analyzing data on an intent-to-treat basis. The primary outcome was psychiatric hospitalization, and secondary outcomes included medical hospitalization and mortality.

The risk of psychiatric hospitalization was 16% lower for patients who started an antidepressant (HR 0.84; CI 0.80–0.88). Patients started on benzodiazepines had a higher risk of psychiatric hospitalization (HR 108; CI 1.02–1.15), while those started on mood stabilizers had an equal risk (HR 0.98; CI 0.94–1.03). Antidepressants were associated with a lower risk of medical hospitalization (HR 0.87; CI 0.79–0.96), whereas no difference was found for benzodiazepines or mood stabilizers. Mood stabilizers were the only group associated with a statistically higher risk of mortality (HR 1.31; CI 1.04–1.66), and this risk was highest with gabapentin.

Both studies had similar weaknesses. With the lack of randomization, various confounding variables could have been overlooked. Factors not examined include reasons for changing medications, frequency of patient-provider contact, use of psychosocial interventions, and extent of medication adherence. Functioning and symptom severity were also not examined. On the other hand, patients prescribed multiple psychotropics are likely to have lower functioning and greater disease severity, so the fact these patients had favorable outcomes is impressive.

TCPR'S TAKE

Polypharmacy is often looked down on, but these results suggest it may be a viable strategy in schizophrenia. In combining antipsychotics, the best outcome was with clozapine and aripiprazole. This suggests prescribing antipsychotics with different receptor profiles may be a useful tactic. In terms of combining antipsychotics with other psychotropics, the results are even less definitive and more likely skewed. That limitation aside, antidepressants appear to have the greatest benefit and least risk. In contrast, mood stabilizers and benzodiazepines should be used with more caution.

—C. Jason Mallo, DO. Dr. Mallo has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

DEPRESSION

An Answer for Psychotic Depression

REVIEW OF: Flint AJ et al, *JAMA* 2019;322(7):622–631

TYPE OF STUDY: Randomized, placebo-controlled trial

Psychotic features in depression indicate a more severe form of the disease, with a higher risk of hospitalization and double the rate of disability compared with non-psychotic depression. A combination of an antipsychotic and an antidepressant is the mainstay of treatment, but how long to continue the antipsychotic is an unanswered question.

This study enrolled patients 18–85 years of age with severe major depression and at least one delusion; hallucinations were optional. Dementia and unstable

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Research Updates Continued from page 6

medical illness were part of the exclusion criteria, so the patients may not have been as ill as some whom we see in clinical practice. Average age was 55 years.

Researchers first treated 269 patients with open-label olanzapine and sertraline. Next, 162 patients who achieved remission or near-remission entered an open-label 8-week stabilization phase. Of the 147 who remained well after the stabilization, 126 were randomized to continue on olanzapine or have the antipsychotic replaced with a placebo for 36 weeks. The design was double blind, and the antipsychotic taper took place over 4 weeks. All patients remained on sertraline throughout the trial.

The primary outcome was risk of relapse, which included relapses into depression or psychosis as well as psychiatric hospitalization or suicidality. 55% of sertraline-placebo patients relapsed, compared to 20% of sertraline-olanzapine patients. The number needed to treat (NNT) to keep patients well with continued antipsychotic therapy was 2.8.

The majority of the relapses (79%) occurred within the first 20 weeks of the 36-week randomization phase. In a letter to the editor, Klaus Munkholm and colleagues argued that these relapses may have been a withdrawal phenomenon. The authors of the study countered that their criteria for relapse shared little in common with known symptoms of antipsychotic withdrawal.

Weight gain was the main side effect of continued olanzapine. The placebo group lost weight while the olanzapine group continued to gain, with a difference of 9 pounds between them at the end of the study. Falls were also greater in the olanzapine-continuation group (31% vs 18%).

TCPR'S TAKE

When a patient recovers from psychotic depression on an antidepressant and antipsychotic, we should continue both medications for at least 2 months as long as the medication is reasonably tolerable. After 6 months of remission (28 weeks), we might consider a slow taper of the antipsychotic, weighing the severity of the episode, side effects, and the patient's preferences.

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

To learn more, listen to our 2/24/20 podcast, "Why Psychotic Depression Matters." Search for "Carlat" on your podcast store.

CME Post-Test

To earn CME or CE credit, you must read the articles and log on to www.TheCarlatReport.com to take the post-test. You must answer 75% of the questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be completed within a year from each issue's publication date. As a subscriber to *TCPR,* you already have a username and password to log onto www.TheCarlatReport.com. To obtain your username and password, please email info@thecarlatreport.com or call 978-499-0583.

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

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

1. According to a 2019 study, the majority of Nuedexta prescriptions have been written for patients with which disorder(s)? (LO #1)
   - [ ] a. Multiple sclerosis and/or traumatic brain injury
   - [ ] b. Amyotrophic lateral sclerosis (ALS) and/or Tourette syndrome
   - [ ] c. Dementia and/or Parkinson's disease
   - [ ] d. Pseudobulbar affect and/or OCD

2. A C-reactive protein (CRP) greater than ____ mg/L is considered to be a marker of high inflammation. (LO #2)
   - [ ] a. 0.5 mg/L
   - [ ] b. 1.25 mg/L
   - [ ] c. 2.5 mg/L
   - [ ] d. 3 mg/L

3. The risk of psychiatric rehospitalization in patients with schizophrenia was 13% lower with polypharmacy than monotherapy, according to the results of a 2019 study. This risk was lowest with the combination of clozapine and aripiprazole. (LO #3)
   - [ ] a. True
   - [ ] b. False

4. According to a 2019 study, which intervention was most effective in reducing aggression and agitation in adults with dementia? (LO #1)
   - [ ] a. Equine therapy
   - [ ] b. Citalopram
   - [ ] c. Music therapy
   - [ ] d. Lorazepam

5. Which of the following is a risk factor for inflammation? (LO #2)
   - [ ] a. Early childhood trauma
   - [ ] b. Low body mass index
   - [ ] c. Low vitamin D levels
   - [ ] d. Childhood-onset OCD

6. In a 2019 study on continuing an antipsychotic medication after psychotic depression responds to treatment, relapses occurred more often in patients taking sertraline-olanzapine than in those taking sertraline-placebo. (LO #3)
   - [ ] a. True
   - [ ] b. False

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Inflammation and Depression
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Next Issue:
Bipolar II
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Learn more and search full archives online:
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In Brief

Price Drop on L-methylfolate. In our August 2019 issue, we compared two supplements that are used to augment antidepressants: folate (0.5 mg to 10 mg/day) and l-methylfolate (15 mg/day). The clinical data pointed toward l-methylfolate, but the price of this supplement put it out of reach for many patients. We've since become aware of a more affordable version of l-methylfolate that's within the price range of folate. Opti-folate 15 mg is $13/month on Amazon.

Expert Interview
Continued from page 5

and tai chi. Those practices are associated with activation of the parasympathetic nervous system, and that in turn reduces inflammation. You can retest CRP after a patient has made those lifestyle changes—it's likely to go down. Antidepressant therapy, on the other hand, does not lower inflammatory markers, even when it's dopaminergic. So it's treating the symptom more than the cause.

TCPR: That sounds like a problem.

Dr. Miller: It's still important to address the inflammation in these patients because inflammation will continue to raise the risk of heart disease, cancer, and other health problems. Of course, those lifestyle changes are easier to make after depression is treated.

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

To learn more, listen to our 2/10/20 podcast, "Inflammation and Depression: An Interview With Dr. Miller." Search for "Carlat" on your podcast store.