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AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

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Learning objectives for this issue:
1. Describe the use of Namzaric, the newest drug for treatment of Alzheimer's disease, along with the effectiveness of older medications. **2.** Explain how to assess and work with patients with cognitive impairment and dementia. **3.** Detail the evidence that benzodiazepines may increase the risk of Alzheimer's disease. **4.** Summarize some of the current findings in the literature regarding psychiatric treatment.

Namzaric and Other Cognitive Enhancers for Dementia

There's a new medication on the market for the treatment of dementia—the first to come along in several years.

In December of 2014, Actavis and Adamas Pharmaceuticals announced the approval of Namzaric, which is a combination of Namenda XR and Aricept, for moderate to severe dementia. While no one would claim that this combination of two existing drugs constitutes a breakthrough in dementia treatment, it may pose some advantages nonetheless.

Before the introduction of Namzaric,

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In Summary

- Patients and families are still waiting for that 'miracle drug' that will stop the progression of memory loss and cognitive decline.
- The medications currently approved for treatment of Alzheimer's disease can slow that progress but are not a cure.
- Namzaric is the newest of the dementia drugs, approved by the FDA in December, 2014.

Q&A With the Expert

Assessing and Working with Patients with Cognitive Impairment and Dementia

Marc Agronin, MD

Geriatric Psychiatrist
Vice President, Behavioral Health and Clinical Research
Miami Jewish Health Systems, Miami, FL

Dr. Agronin has disclosed that he is principal investigator on research grants from several pharmaceutical firms and that all funds go directly to his employer, Miami Jewish Health Systems. In addition, he has been on the speakers bureaus of Forest Laboratories (Namenda XR), AssurX (GeneSightRX), and Novartis (Exelon Patch). Dr. Carlat has reviewed the content of the interview and has determined that there is no bias due to these relationships.

TCPR: Dr. Agronin, as someone who does a lot of evaluations of elderly patients, what is your overall approach in working with patients who present with cognitive issues?

Dr. Agronin: The first priority is to establish some rapport with the person and his or her caregiver. I emphasize the caregiver because if you don't have a reliable informant you simply will not be able to do an accurate evaluation. There is a tremendous amount of uncertainty and misdiagnosis; it is a very complex evaluation to do for several reasons. Number one is that we have no simple, reliable, accurate test as of today to make a diagnosis of Alzheimer's disease or any other neurocognitive disorder. We are getting closer, but when you look at the accuracy rates for Alzheimer's disease, for example, it depends on looking at multiple sources of data over time. To me that relies on having some rapport with the individual so you can get a sense of the whole range of their strengths and limitations. You can get the most accurate information from the caregivers, and that helps put together

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the last truly new medication, memantine (Namenda), was approved in 2003. Before that, we had the approvals of donepezil (Aricept) in 1996, rivastigmine (Exelon) in 2000, and galantamine (Razadyne) in 2001. What followed have been old medications in a new format (Exelon Patch in 2001, Aricept ODT in 2004, Razadyne ER in 2004, Namenda XR in 2010, and high dose Aricept in 2010).

A Review of the Old and New

In this article we'll take a look at the Namzaric data and come up with some recommendations. But first let's do a quick review of the evidence for the meds that are already available.

We organize the meds by stage of illness (mild to moderate vs. moderate to severe), because this is how the US Food and Drug Administration (FDA) approves them. However, real patients don't easily fit into such categories, and real psychiatrists will use their best judgment regarding prescriptions. That often means going off-label—for example, prescribing cognitive enhancers for non-Alzheimer's dementias, or prescribing Namenda for patients who may not quite meet formal criteria for "moderate to severe" dementia. Use the "my grandmother" rule to guide your decisions—if this patient were your grandmother (or other loved one), what would you do? Because there are so few treatments for dementia, you'd likely stray beyond FDA guidelines in the quest for a good result.

Mild to Moderate Dementia

Four different acetylcholinesterase inhibitors (AChEIs) have been approved for mild to moderate dementia: Tacrine (remember Cognex?) was the first but is no longer used due to liver toxicity; then came Aricept, and later Aricept ODT; Exelon and Exelon Patch; and Razadyne and Razadyne ER.

To test the effectiveness of any drug, you have to define an outcome of interest and see if the drug improves it relative to placebo. Most studies of Alzheimer's disease (AD) rely on the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog), a 70-point scale that tests memory, language, orientation, and praxis (ability to carry out simple motor skills). Scores range from 0 to 70—the higher the score, the worse the impairment. Patients with mild to moderate dementia typically have ADAS-Cog scores between 15 and 55.

How well do AChEIs work? First of all, these drugs rarely actually improve cognition—instead, they act by reducing the rate of cognitive worsening. Without medications, an average patient with mild AD may experience an increase (worsening) of 5 ADAS-Cog points in a year. AChEIs slow this rise by 2 to 3 points relative to placebo (this is confusingly reported in article abstracts as a "decline" in the ADAS-Cog, when what is meant is a diminution in the rise of the ADAS-Cog as compared to placebo).

What does a 2 to 3 point difference mean clinically? According to one study, a minimum of a 3 point difference is required before a clinician notices that there is a meaningful improvement (Schrag A et al, *J Neurol Neurosurg Psychiatry* 2012;83:171–173). A 3 point difference might translate to, for example, a patient remembering who came to dinner the night before or being able to dress himself (Boustani M et al, *Ann Intern Med* 2003;138(11):927–937). The bottom line is that AChEIs beat placebo by a small amount—statistically significant but not always clinically significant.

Moderate to Severe Dementia

Three medications have been approved for moderate to severe dementia: Namenda (along with its patent-extending offspring, Namenda XR), Aricept 23 mg, and Namzaric, the Namenda/Aricept combo product.

Namenda, Namenda XR. Namenda (approved in 2003) and Namenda XR (2010) are N-methyl-D-aspartate (NMDA) antagonists that are both approved for moderate to severe AD based on six-month clinical trials showing small but statistically significant benefit over placebo (Kurz A & Grimmer T, *Expert Opin Pharmacother* 2014;15(13):1955–1960). As with AChEIs, Namenda will neither reverse nor halt the cognitive decline but may slow it down. It's pretty well tolerated, with headache, dizziness, and dose-related somnolence most commonly reported.

Its manufacturer Forest Laboratories' marketing pitch for Namenda XR is that once a day dosing increases convenience and compliance. The company initially announced that it would be discontinuing regular Namenda (available in 5 mg and 10 mg tablets), forcing patients to switch to Namenda XR (available in 7 mg, 14 mg, 21 mg, and 28 mg) if they want to keep taking it. The reasons are economic: old Namenda's patent is expiring, and the company wants to get patients on their new branded version before generic memantine hits the market. The tactic (called the "forced switch") has been successfully used by other companies in the past, for better or worse. The New York State attorney general is suing the company for violating anti-trust laws, so for now, the company is continuing to make the IR available under the terms of a court order.

Aricept 23 mg. In 2010, just before the original Aricept went off patent, the

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FDA approved higher dose Aricept for moderate to severe dementia—at an odd dose of 23 mg. It was a controversial approval (for the fascinating inside story, see Schwartz LM & Woloshin S, *BMJ* 2012;344:e1086).

The pivotal study randomly assigned 1,400 patients with moderate to severe dementia to either Aricept 23 mg per day or Aricept 10 mg per day. Mindful that a dementia drug can beat its competitor on a numerical cognitive scale without yielding true clinical benefit, the FDA told Eisai (the manufacturer) that its drug would have to show superiority on two scales—a cognitive scale and global functioning scale. After six months, the results were tallied, and 23 mg beat 10 mg on only one of the measures—by a mere 2.2 points out of a 100 point severe symptom scale. Furthermore, the higher dose caused significantly more side effects than the lower dose, particularly nausea (12% vs. 3%) and vomiting (9% vs. 2.5%). Because of these issues, the FDA review team recommended non-approval, but that decision was overridden by the director of the FDA's neurology division.

Namzaric (Namenda plus Aricept). Now we've circled back to Namzaric, which received FDA approval in 2014. Namzaric is a combination of Namenda XR and Aricept (available in two doses: 28mg/10 mg and 14mg/10 mg, Namenda XR/Aricept). The rationale for combining these two medications is that since each one is somewhat effective for moderate to severe dementia and since they have different mechanisms of action, combining them should be even more effective.

In the pivotal Namzaric study, 677 outpatients with moderate to severe AD, who were already stable on an AChEI (mostly Aricept), were randomized to 24 weeks of add-on Namenda XR 28 mg or add-on placebo (Grossberg GT et al, *CNS Drugs* 2013;27(6):469–478). Patients on the active combination did better than those on an AChEI plus placebo, with higher cognition scores but no difference on activities of daily living scores.

Comparing Dementia Medications

Generic name (Brand name)	Usual daily dose
Mild to Moderate AD	
Donepezil (Aricept, Aricept ODT)	5–10 mg QD
Galantamine (Razadyne, Razadyne ER)	16–24 mg (divided BID for IR, QD for ER)
Rivastigmine (Exelon, Exelon Patch)	3–6 mg BID; or 4.6, 9.5, or 13.3 mg/24 hour patch QD
Moderate to Severe AD	
Donepezil (Aricept)	10–23 mg QD
Memantine (Namenda, Namenda XR)	10 mg BID or 28 mg XR QD
Memantine XR/donepezil (Namzaric)	28/10 mg QD (14/10 mg in renal impairment)

DR. CARLAT'S VERDICT: For mild to moderate AD, start with an AChEI—we have the most data and experience with Aricept but the others are equally effective. You want to titrate Aricept to an effective dose, which according to FDA guidelines maxes out at 10 mg/day, but patients may tolerate 15 mg to 20 mg a day (Doody RS et al, *Drugs Aging* 2008;25(2):163–174). For moderate to severe AD, start with Namenda IR, reserving the more expensive Namenda XR for those rare situations in which IR is poorly tolerated. Or use high dose Aricept (either combining two 10 mgs or using the 23 mg version). A more common approach among experts is to stabilize patients on an AChEI, then add Namenda, regardless of whether the dementia is mild, moderate, or severe. For patients who have trouble taking two pills, consider Namzaric. Regardless of what you use, remind patients and their caregivers that these medications do not reverse or stop the decline associated with AD—they just slow it down a little.

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Expert Interview

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the story. The other thing is that unlike many other disease states we can't look at tissue; we don't do a brain biopsy per routine, and even with the new imaging it only approximates what we are trying to look at in the brain. I have learned this lesson when we have done several clinical trials that involved autopsies, and the postmortem results of the brain biopsy are always a whole grab bag of different pathology. In several cases, the results were not consistent with what we thought the patient had after years of observation.

TCPR: Let's say a patient comes in to the psychiatrist's office complaining that his memory isn't what it once was and he is worried that he has Alzheimer's disease. How should the psychiatrist proceed?

Dr. Agronin: Memory concerns should always be taken seriously and psychiatrists should be able to do a basic workup. Obviously, the older the person is, the more likely there might be a memory disorder. But at any age, it is very important that we do an evaluation that includes basic lab work, an examination, and some questions about changes in mood and daily function—such as sleep and appetite—just to get a sense of whether there is depression or anxiety that could be a contributing factor. Psychiatrists should always ask about substance use because lots of older individuals are drinking more alcohol than they should be or that they may admit to. I find that this is often a hidden factor and sometimes, without an informant, you are not getting a clear history.

TCPR: If somebody is drinking, is the memory problem limited to the times when they are intoxicated or hung over, or does it extend to other periods as well?

Dr. Agronin: Well it depends. If someone has memory issues, often what happens is that they have their one cocktail and then an hour or two later they have what to them is their one cocktail because they have forgotten that they've had one before. I find, espe-

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cially in couples in which this is a lifelong habit, the partner often doesn't notice that there is an issue or a problem and they might even be part of it. There may be reversible factors that are either causing or worsening the memory issue, which can be addressed. With drinking, if there is no underlying brain pathology, memory problems may just extend to the time around which they are drinking. But individuals who are drinking more than they should have higher rates of falling and injury, which can contribute to memory problems. And, while alcohol might help people fall asleep initially, it disrupts sleep architecture and that, in turn, can have a negative impact on memory. Also, a lot of individuals are taking anxiolytics and/or sleeping pills at the same time they are drinking alcohol, so you can have an additive effect. This is why you need to review all medications. Sometimes statin medications in a small percentage of people can cause some mental fuzziness. Narcotics and anticholinergic medications also can have significant effects on memory.

TCPR: You mentioned labs. Go through with us the basic labs that should be ordered in a workup.

Dr. Agronin: In general, it is rare to find a lab value correlating with a cognitive disorder. But what you are looking for are lab abnormalities that point to certain conditions—severe anemia, hypothyroidism, and parathyroid issues such as an adenoma leading to excess calcium in the blood—all of which can lead to some cognitive problems. If someone is diabetic, I would look into how well their blood sugar is controlled, and hypertension might indicate that someone is having small strokes. Individuals with both hypertension and diabetes are some of the highest risk individuals for vascular dementia and Alzheimer's disease. So these are everyday factors that can loom very large in terms of causes, or probably more likely, exacerbating factors.

TCPR: So we do our basic labs and we don't find anything obvious. The patient is complaining of some kind of memory loss. How do we determine if this is a normal part of aging, mild cognitive impairment, or early Alzheimer's dementia?

Dr. Agronin: In early stages, it can be impossible to know. So for psychiatrists, what I recommend is to have some screening instrument: either the Mini-Mental Status Examination (MMSE), the Montreal Cognitive Assessment (MOCA), or the Mini-Cog. Have someone in the office trained to conduct the screening so they do it consistently and can be rather expeditious with it. If someone fails the Mini-Cog, or if on the MMSE or the MOCA they are scoring below 25 to 26 or they have a higher score but they have very significant complaints, then I would refer them to either a memory center or a geriatric psychiatrist or neurologist who specializes in neurocognitive disorders to do a more thorough evaluation. The important things for psychiatrists to look for would be: is there any depression or anxiety that might be compromising memory or other cognitive function? Individuals with severe depression can have a pseudodementia in which their concentration and attention and motivation are so poor due to the depression that their memory suffers as well. With those individuals, once you successfully treat the depression, their memory should get better. Though it should be noted that some research indicates that they are at a much higher risk for later developing dementia or that depression may itself be a prodromal symptom of neurocognitive disorders including Alzheimer's disease (Alexopoulos GS et al, *Am J Psychiatry* 1993;150(11):1693–1699). It's important for clinicians to realize that even if there is depression and even if it does appear to be affecting cognition, it still might be comorbid with an actual neurocognitive disorder. Sometimes the mistake that psychiatrists make in these cases is that they put someone on an antidepressant, but they may not follow up quickly enough and deeply enough to assess cognition once they have had a trial of the antidepressant. Often the depression goes hand-in-hand with Alzheimer's disease or some other neurocognitive disorder.

TCPR: What kind of neuroimaging should these patients have?

Dr. Agronin: An MRI is always best because it will show everything that you are looking for on a CT scan, but will also pick up smaller subcortical lesions. And what I am looking for, especially in more acute onset of cognitive changes, would be meningiomas, subdural hematomas, and lacunar infarcts.

TCPR: So we've done the labs and neuroimaging and nothing jumps out in terms of comorbid depression, or substance abuse, or anything else that's obvious. You now have a patient with some degree of cognitive impairment but no clear cause. What's next in the evaluation?

Dr. Agronin: Neuropsychological testing is pretty much the gold standard in terms of knowing whether there is any significant cognitive impairment and what is the extent of it.

TCPR: Do we send everyone who comes in complaining of memory issues to neuropsych testing?

Dr. Agronin: Not necessarily. If I meet with someone and find that there is just mild intermittent forgetfulness and they are very articulate about what they are forgetting, I am less concerned. I am more concerned about someone who is not aware of forgetfulness, or not aware of being repetitive and the informant is telling you that, or you are seeing changes outside of memory such as word-finding difficulty, disorientation, visual-spatial changes—I would order testing in any of these kinds of patients. But even if you decide to hold off on neuropsych testing, I would reassess what is going on after three to six months and if there are persistent problems or changes, then I think you are obligated to get a neuropsychological profile done.

If you can make certain that their lifestyle is healthy—getting enough exercise, a good diet, having appropriate supervision, not doing dangerous things that are going to cause more problems—they are going to do better in the long run.

Marc Agronin, MD

TCPR: And what are you likely to find on neuropsych testing?

Dr. Agronin: Technically speaking, neuropsychological testing should show that they are at least about a standard deviation below their peers as the formal criteria for mild cognitive impairment (MCI). In practice, if we see someone who has persistent memory

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Benzodiazepine Use and Alzheimer's Risk

If you're like most psychiatrists, you get your fair share of older folks who come into the office complaining of difficulties with sleep or with significant symptoms of anxiety.

In many of these cases, after an adequate workup, it's not unusual to use at least a short course of benzodiazepines such as Restoril or Ativan. We've known for some time that we need to be particularly careful about using benzos in older patients because of the increased fall risk (Hill KD & Wee R, *Drugs Aging* 2012;29(1):15–30) but we now have increasing evidence that these meds may increase the risk of Alzheimer's disease (AD).

The latest study to document this association is the largest and most convincing one yet. Researchers looked through health insurance data from Canada, and located the records of 1,796 patients who had developed AD. They ascertained what percentage of these patients had used benzodiazepines over the past six years. They then collected records for a comparison group of 7,184 elderly patients who were cognitively normal and extracted the same benzodiazepine data.

The question was whether patients with AD were more likely to have used benzos than the patients without AD. That answer was yes: those with a history of benzo use had a 51% increased risk for AD. Even when they adjusted for potential confounders such as depression, anxiety, and insomnia, the results did not change by much—there was still a 43% increased risk.

They also found that the higher the number of doses used, the higher the AD risk. For example, looking at only the group who used fewer than 180 doses, the risk was increased by 84%. On the other hand, patients who used fewer than 90 doses had no increased risk, and the middle group of 90–180 doses had an in between risk. Also, long-acting benzos conferred a higher risk than short-acting benzos (70% vs. 43%) (Billioti de Gage S et al, *BMJ* 2014;349:g5205).

DR. CARLAT'S VERDICT: While this is not the first study to show an association between benzo use and dementia, it is the most rigorous study and the first to show a correlation between cumulative dose exposure and risk of AD. Correlation does not equal causation, but the results do encourage us to use common sense in prescribing benzos to the elderly—minimize the dose and stick with shorter acting agents when possible.

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changes that are a nuisance but they are still functioning pretty well, we usually will label that MCI as a provisional diagnosis, with or without testing.

TCPR: Let's say the neuropsych testing comes back a standard deviation below the norm and the report says something about mild cognitive impairment. How do you communicate that to the patient without being overly alarmist while at the same time providing an accurate picture?

Dr. Agronin: I meet with them and I basically lay all the puzzle pieces out on the table. I will recap the history that they reported to me, factor in any medical issues, any medication issues, and psychiatric issues that might be a concern and what the neuroimaging showed. I will then bring in the neuropsychological test results and we look at the big picture and I will give them an impression based on that. I may say, "When we look at your history of slow but steady cognitive decline over the last year or two, we haven't identified any specific factors that appear to be causing this. For instance, the brain scan didn't show anything different than a normally aged brain. The neuropsychological testing showed memory impairment more than we would expect relative to your age, and the concern is that this may be early Alzheimer's disease. We can't say this with certainty and we have to monitor you over time. We are here to work with you, to be a partner with you, to follow you over time. And we can also talk about some of the different treatment options ranging from lifestyle changes—what we call brain healthy lifestyle—to cognitive enhancement medications to clinical trials."

TCPR: I am going to pretend I'm the patient here. "Does this mean I have dementia and why can't you tell me for sure?"

Dr. Agronin: I would explain, "The information indicates what we call a neurocognitive disorder and of the different types, it is most consistent with early stage Alzheimer's disease. The only way to know with 100% certainty is you have to actually look at the brain tissue and obviously we are not going to do that here."

TCPR: Then the patient might ask, "What does this mean in terms of my future? Does this mean that next year I am not going to be able to do anything?"

Dr. Agronin: I would then say, "Well, if this is Alzheimer's disease we know that it is a progressive illness. I would liken it to a glacier moving. It is very, very slow; the changes unfold differently for different individuals. We don't have a cure for it, but there is a tremendous amount we can do to not only lessen the impact of other factors that can worsen it, but there are also some symptomatic treatments we can consider and there are also clinical trials that might offer the hope of slowing down the course of the disease itself." At this stage of the disease I emphasize with individuals that we are going to work together and we will address every management issue. I don't get into details about later stages of it because I think that may only worry individuals and I don't think it is helpful to the discussion. For someone with early stage Alzheimer's disease, if you can address anxiety and depression in both them and the caregiver, they do better. If you can help them understand the benefits and limitations of a cognitive enhancing regimen, they will be more likely to adhere to it and to maximize its benefits. If you can make certain that their lifestyle is healthy—getting enough exercise, a good diet, having appropriate supervision, not doing dangerous things that are going to cause more problems—

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Research Updates IN PSYCHIATRY

DEMENTIA

Anticholinergics and Dementia

Many medications have anticholinergic side effects, which can be particularly troublesome for the elderly—such side effects include tachycardia, urinary retention, cognitive impairment, and in the extreme cases, delirium.

Nonetheless, such meds are still used quite widely in older patients for problems such as insomnia, depression, allergies, overactive bladder, and neuropathy. One report found that 37% of the elderly are taking meds with anticholinergic properties. A large, new study provides the strongest evidence yet that anticholinergics may increase the risk of dementia.

A total of 3,434 adults over 65 years of age from the National Institute on Aging-funded Adult Changes in Thought (ACT) study were enrolled. The mean age was 74.4 years, 60% were women, 91% were white, and about two-thirds had some college education. Pharmacy dispensing data were used to determine anticholinergic drug use as far as 10 years prior to study entry. The medications used in the most recent one-year period were excluded to avoid bias (often, anticholinergic antidepressants may be used to manage early symptoms of dementia, including prodromal insomnia or depression).

Over 78% of subjects had taken an anticholinergic drug in the 10 years prior to study entry. The medication doses were standardized and converted into an anticholinergic exposure measure indicating the overall anticholinergic burden. Cognitive function was assessed using the Cognitive Abilities Screening Instrument at study entry (anyone with dementia was excluded) and then biennially. For those whose assessment indicated some cognitive impairment, further evaluation for dementia was conducted including physical and neurological exams and neuropsych testing. Dementia diagnosis was made based on clinical consensus of a multidisciplinary team.

The researchers found that 23.2% of subjects developed dementia (mostly Alzheimer's disease) after a mean follow-up of 7.3 years. The subjects who were in the highest anticholinergic exposure category had a statistically significant increased risk for dementia compare with those with no anticholinergic use (examples of high exposure include taking of 50 mg/d of Benadryl for six months, 10mg/d of Doxepin for nine months, and 5 mg/d of Zyprexa for 12 months). Those with less exposure still had a slightly elevated risk for dementia.

One of the more interesting findings was that the timing of heavy anticholinergic use within that 10-year exposure window was not important—those who used anticholinergics cumulatively over a long period in the past had as much risk as those who had more recent continuous use of anticholinergics (Gray SL et al, *JAMA Intern Med* 2015;Epub ahead of print).

TCPR's Take: This study showed a clear association between anticholinergic use in the elderly and later development of dementia. Correlation does not necessarily imply causation. For example, the elderly who took most anticholinergics may have been destined to develop dementia irrespective of the medications. It's possible that a person with "pre-dementia" happens to have other symptoms, such as insomnia or depression, which lead their doctors to prescribe drugs with anticholinergic side effects. Nonetheless, this is the first study to show a cumulative dose association and it is also the first to suggest that dementia risk linked to anticholinergic medications may persist even years after people stop taking these drugs. Think about this as a modifiable risk factor and minimize total anticholinergic burden in your older patients when alternatives are available.

EXERCISE

Intensive Weight Loss Program for Psychiatric Patients Yields Mediocre Results

We know that several commonly used antipsychotics cause weight gain (yes, we're looking at you, Zyprexa, Risperdal, and Seroquel)—but we don't know much about how to prevent the side effect, or how to treat it once it occurs. A recent study tested an intensive weight loss program in a large group of psychiatric patients. The results were… well, read on and you decide whether they were impressive.

The researchers enrolled 181 overweight psychiatric patients from health clinics in the Pacific Northwest. To be included in the study, patients had to be at least 18, had to have been on an antipsychotic for at least 30 days prior to entry, and had to be at least moderately overweight, with a minimum body mass index (BMI) of 27. Most of the patients who enrolled were actually much heavier than "moderately overweight"—their average BMI was 38, and their average weight was about 108 kg, or nearly 240 pounds. Most patients had a diagnosis of either bipolar disorder/affective psychosis (69%) or schizophrenia spectrum (29%).

Patients were randomly assigned to one of two groups: the STRIDE weight loss program or standard psychiatric care without any specific weight loss focus. STRIDE participants attended weekly two-hour group meetings for six months, exercised for at least 20 minutes daily, and received nutrition and behavior modification counseling. They were also required to maintain daily food and sleep diaries. After the six month intervention phase, patients entered a six month maintenance phase that was less intensive, consisting of one meeting per month.

So did STRIDE work? At baseline, the average weight of the STRIDE participants (n = 93) was 238.9 pounds. After six months, they lost 9.3 pounds (3.9% of initial weight), to weigh in at 229.6 pounds. The control group (n = 85), by contrast, *gained* a little weight: they went from 234.5 pounds to 236.6 pounds, for a weight gain of 2.1 pounds (0.9%). The weight difference between intervention and control was statistically significant. Unfortunately, the benefits of STRIDE lessened after another six months. While the STRIDE participants basically maintained their lower weight during the maintenance phase, the control group lost some weight, so that 12 months after

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CME Post-Test

This CME post-test is intended for participants only seeking AMA PRA Category 1 Credit™. For those seeking ABPN self-assessment (MOC) credit, a 13 question pre- and post-test must be taken online. For all others, 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 at least four questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be taken by March 31, 2016. As a subscriber to *TCPR,* you already have a username and password to log on www.TheCarlatReport.com. To obtain your username and password or if you cannot take the test online, please email info@thecarlatreport.com or call 978-499-0583.

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

1. Which of the following is true about Namzaric (Learning Objective #1)?
   - [ ] a) It is a breakthrough medication that appears to stop cognitive decline
   - [ ] b) The newest dementia medication, it is a combination of Namenda XR and Aricept
   - [ ] c) It is only for treatment of mild dementia
   - [ ] d) The FDA approved it in 2013
2. There is currently no simple, reliable, accurate test to make a diagnosis of Alzheimer's disease (AD) or any other neurocognitive disorder (LO #2).
   - [ ] a) True [ ] b) False
3. What kind of neuroimaging should be ordered to help diagnose patients with cognitive decline (LO #2)?
   - [ ] a) X-ray [ ] b) CT scan [ ] c) MRI [ ] d) Cerebral angiography
4. A Canadian study that looked at the relationship between benzodiazepines and the risk of Alzheimer's disease (AD) found which of the following results (LO #3)?
   - [ ] a) Patients with a history of benzo use had a 51% increased risk for AD
   - [ ] b) Patients with a history of benzo use had a 43% decreased risk for AD
   - [ ] c) The higher the number of doses of benzos, the lower the AD risk
   - [ ] d) Shorter-acting benzos conferred a higher risk of AD
5. A study that looked at the use of medications with anticholinergic properties and the risk of dementia, found which of the following was true (LO #4)?
   - [ ] a) There was no relationship between anticholinergics and risk of dementia
   - [ ] b) Those who had high anticholinergic exposure had an increased risk of dementia
   - [ ] c) Those with less exposure had no risk at all for dementia
   - [ ] d) The risk was only for those who took Doxepin

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Expert Interview

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they are going to do better in the long run. This is just the tip of the iceberg in terms of management issues so I work with a whole team. I have a neuropsychologist, a social worker, research staff, and support staff to enwrap the patient and their caregivers in a supportive system and I find that everyone does better over time when you take this approach.

TCPR: What is your approach to prescribing cognitive enhancers and explaining to patients what they can expect in terms of efficacy?

Dr. Agronin: Well, what I tell patients is that there are a number of cognitive enhancing medications that are approved by the US Food and Drug Administration, but they are not cures. In general, what the data indicate is that people tend to do better on them than off of them so it is worth a trial. We are doing this over the long haul because this is a disease that can go on for a decade or more. I will start one of the acetylcholinesterase inhibitors and I will make sure I maximize the dose because if you don't, you are simply not getting the benefit from it. Then once they are stabilized and if they are tolerating it, I will add memantine (Namenda). For more on medications, see "Namzaric and Other Cognitive Enhancers for Dementia" on p. 1).

TCPR: How long do you continue using the dementia medications?

Dr. Agronin: There are limited data showing that you get the same benefit with some of the acetylcholinesterase inhibitors over years and not just the several months that most clinical trials look at (Rountree SD et al, *Alzheimers Res Ther* 2009;1(2):7). In clinical practice, that has been my experience and my impression, so I continue people on them for the duration. I have had a few instances where in later stages when you stop the medication, sometimes you can get declines or changes and that it is hard to get back to their previous baseline if you restart it. You know, arguably, the benefit you get in later stages is quite modest. There are diminishing returns with these medications as you progress in disease because you just have fewer cells that even are producing acetylcholine. If someone is in a terminal phase, it is usually appropriate to withdraw the medication because you might not be seeing any benefit at that point. I take just a very practical approach to it. I want to emphasize that, to me, the use of medications is within the whole context of working with the person and treating them.

TCPR: Thank you, Dr. Agronin.

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Research Updates

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study entry, there was only a 5.7 pound difference between the two groups—which barely achieved statistical significance.

Researchers also measured various labs, but only one of them—fasting blood glucose—decreased more in the intervention group at 12 months. There were no significant differences between the groups in triglycerides, LDL, HDL, or blood pressure readings (Green CA et al, *Am J Psychiatry* 2015;172(1):71–81).

TCPR's Take: While any weight loss is better than none, the results of this intervention were somewhat disappointing. In round numbers, markedly obese patients (eg, about 240 pounds) stand to lose about 4% of their body weight after a year if they participate in a highly structured six-month weight loss program—vs. about 2% of their weight if they simply go to regular doctor appointments. In fairness, as the authors point out, not all patients took the program seriously, and those who attended more sessions and filled out more food logs lost more weight.

So the positive spin on the study is that highly motivated obese patients are likely to lose a bit of weight in a STRIDE-like program. But it's likely that a much more effective strategy is prevention—and we can help by prescribing weight-neutral medications when possible.

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