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Chris Aiken, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Race and Mental Health

Learning Objectives

After reading these articles, you should be able to:

1. Describe how to use varenicline for smoking cessation.
2. Identify patients appropriate for tricyclic antidepressants.
3. Provide culturally competent treatment to patients.

How to Use Varenicline (Chantix)

Steven A. Wyatt, DO. Adjunct faculty, University of North Carolina at Charlotte.

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

Henry is a 45-year-old married man with anxiety and alcohol use disorder who smokes a pack a day. He has tried nicotine replacement in the past but was unsuccessful. His alcohol use has stabilized in recent months, and he believes he is ready to make another attempt at quitting smoking.

There are three medications with FDA approval for nicotine dependence: Nicotine replacement therapies, bupropion, and varenicline. Varenicline (Chantix) is arguably the most effective, but cost and concerns about neuropsychiatric side effects have limited its use, and a recent recall of the product temporarily stopped it entirely.

Highlights From This Issue

Varenicline (Chantix) is back on the market—in generic form—and it's one of the most effective meds we have for nicotine cessation.

Microaggressions, implicit bias, drapetomania, and more . . . Dr. Kali Cyrus details the concepts you need to know about race and psychiatry.

When you're ready to use a tricyclic for depression, nortriptyline is a good starting point, and the serum levels of this drug are worth following.

In September 2021, Pfizer voluntarily pulled branded Chantix from the market due to contamination with nitrosamines, a carcinogen that has tainted the production of numerous medications in recent years, including ranitidine, nizatidine, and metformin.

Continued on page 4

Q&A With the Expert

Racism and Psychiatry
Kali D. Cyrus, MD, MPH

Assistant professor, Department of Psychiatry, Johns Hopkins Medicine, Baltimore, MD. Physician-activist in private practice, Washington, DC.

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

TCPR: What does a psychiatrist need to know about race in this era?

Dr. Cyrus: Race and identity are hot topics, even for White people, so psychiatrists need to find a better way to talk about it. The pandemic brought the dynamics of oppression and inequality to the forefront in medicine. Racism is not just happening in the news, the protests, and the Black Lives Matter movement.

TCPR: Has psychiatry contributed to the history of racism in this country?

Dr. Cyrus: Psychiatry and medicine in general have not always been kind to people who are on the margins, people who are not White, people who are not cisgender, and people who are not able bodied or native English

Continued on page 2

Expert Interview

Continued from page 1

speakers. Historically, we've done things like experimenting on certain people who look a certain way or deliberately not explaining what we are doing or even telling them the opposite of what we are doing. For example, my patients comment often about being given a medication without much explanation, which leads to them not trusting the doctor or the psychiatric field. It helps to go the extra mile in explaining side effects, how the medication works, and the reason you're recommending it.

TCPR: Some of these problems in psychiatry go way back, like drapetomania. Is that still relevant today?

Dr. Cyrus: Yes, it may be on the minds of some patients, either directly or indirectly. Drapetomania was a diagnosis applied to people who resisted slavery. It was referred to as a "mania for freedom" (Bailey ZD et al, *N Engl J Med* 2021;384(8):768–773). Samuel Cartwright invented the term in 1851. He also coined "dysaesthesia aethiopica" to explain enslaved people who had lost their motivation to work. Dr. Cartwright apprenticed under Benjamin Rush, whose image is on the seal of the American Psychiatric Association. It's a reminder that we need to think about who created the standards for how we diagnose.

TCPR: What about involuntary hospitalization? Has that affected the Black community in certain ways?

Dr. Cyrus: That's a good question, particularly today when so many states use the police to transport patients to psychiatric hospitals. We have a long history of overdiagnosing schizophrenia in Black males. We tend to go to the psychotic instead of the mood or bipolar category in that population (Gara MA et al, *Psychiatr Serv* 2019;70(2):130–134). Psychiatrists are also more likely to interpret Black patients as aggressive, and these biases have probably led to more involuntary hospitalizations in this group.

"Talk to people who are from different walks of life and learn from them. It's not just the words we use, but everything down to how we design our office space. Are we making people who are different from us feel welcomed? What about the magazines and decor in our waiting rooms?"

Kali D. Cyrus, MD, MPH

TCPR: How is this playing out in your practice?

Dr. Cyrus: Like with most mainstream events, I have seen external racial conflicts show up internally with my patients in both subtle and obvious ways. I had one patient who believed that President Trump sent the Secret Service after them because they were Black. Another feared going to the mall because there could be a shooter targeting Black people. Many of my current patients fear having to go back to the office to interact with their White colleagues. Much of their time in session is spent ruminating over distressing encounters involving White people. They present with insomnia, irritability, isolation, and apathy related to having to go to work, go to the grocery store, and generally interact with the larger world that puts them in a position to be discriminated against.

TCPR: Are more Black people seeking psychiatric help?

Dr. Cyrus: Since the pandemic, there's been a surge in psychiatric visits in general. My experience is that Black people are included in this surge. They often tell me, "This is the first time I have seen a psychiatrist," despite needing to see one for years. The pandemic's events have made people more aware of problems that have simmered for decades. They see things on the news that have happened to them, their loved ones, or people who look like them. And watching harmful things happen makes people wonder whether trouble will knock on their door too—which has driven many to seek help (Brandow CL and Swarbrick M, *Psychiatr Serv* 2021 (Epub ahead of print)).

TCPR: They are seeing people who look like them get abused or killed by the police. What effect does that have?

Dr. Cyrus: When you start to see these images of Black people being killed, you worry that it will happen to you. And it's not just the police. They are seeing incidents where armed citizens have gone out of their way to harm people out of some perceived fear—Trayvon Martin, Ahmaud Arbery, and the actions of Kyle Rittenhouse. At that point, the violence starts to feel more arbitrary, and you don't know where it is coming from or if it

Continued on page 3

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Expert Interview

Continued from page 2

could happen to you. For me, this means avoiding places that are mostly populated by White people or making sure I'm with someone who can be a witness if I do go to those places. Racism is not just a collection of negative experiences here and there. It can feel like an ever-present, bodily fear that you have no way to protect yourself from.

TCPR: Are some areas of the country more affected than others?

Dr. Cyrus: Racism and oppression happen everywhere—in liberal and conservative circles, in the South and California, and across health care settings. However, many people (myself included) use characteristics of an area to assess risk. For example, I live in DC, and if I am going on a road trip, I am much more careful and anxious while driving through states that have more conservative voting records, more flexible gun laws, and confederate flags hanging from the windows. While it's statistically unlikely that something will happen to me because I am Black, I still have the stories of Ahmaud Arbery and Sandra Bland burned in my memory. The fear feels very real, and this reaction is very normal in the Black community.

Examples of Microaggressions

Microaggression	Implicit Message
"Where are you from?" "You speak good English."	You are not an American.
"You are so articulate." "You are a credit to your race."	People of color are not as intelligent as Whites.
"There is only one race: the human race."	Other ethnic experiences do not matter.
Asking a Black person to speak calmly and quietly, or an Asian person to speak up.	You must assimilate to the dominant culture.
"Everyone can succeed in this society if they work hard enough."	People of color are lazy and need to work harder.
"I'm not a racist. I have several Black friends."	Racism and implicit bias have no societal impact.
Walking away from or protecting oneself around people of color.	You are a criminal.

TCPR: The divisiveness in society has raised the lid. Are you saying it has also made life feel less safe for non-White Americans?

Dr. Cyrus: Yes. It's raised the lid without giving us the tools to repair. COVID-19 has added to the problem because we've been living apart under quarantine, and now we're trying to figure out how to interact with each other again. Many Americans with oppressed identities don't have a voice and are not in a position to explain everything. So what do they do? They talk with each other, and they talk on the internet.

TCPR: To talk, you need language. Can you bring us up to date on the new language that's being used around these issues?

Dr. Cyrus: One term you'll hear used a lot is implicit bias. This is when you can't directly report how you feel about a certain group of people, but you have an unconscious preference for or against them. And when that bias is negative, it often feels to the victim like a microaggression, which is another term to know (FitzGerald C and Hurst S, *BMC Med Ethics* 2017;18(1):19). Microaggressions are everyday slights that may happen when you're talking to another person, like misgendering them or calling them by a different name. *(Editor's note: See table on this page)*

TCPR: Sounds like microaggressions are very common.

Dr. Cyrus: Yes. Most minorities have experienced them, but it doesn't mean your patient will recognize them. To get by in society, they've had to brush them off and pretend they didn't happen. Now that we're talking more about racism and oppression, people who were once in denial about racist experiences are starting to recognize the impact those experiences have had on their lives. I also want to explain a bit more about racism, as there are a few more terms to know. Racism is discrimination that takes away resources from a group, based on race, that doesn't have the same access to help as other groups. That discrimination can happen to other groups, like women, the differently abled, and Jewish people, and we call that sexism, ableism, or antisemitism. There are three levels of these "isms": *internalized, interpersonal,* and *systemic*.

TCPR: Let's go through those. What is internalized racism?

Dr. Cyrus: Internalized racism is insidious, and it shows up in practice. Essentially, it is accepting the negative messages you've heard about your identity. It's almost like a self-hatred that can take varying levels of intensity, like feeling embarrassed, ashamed, or angry. People feel "lesser than," especially in places where they are being evaluated, like on a date or at work. They don't speak up because they fear being perceived as less intelligent. They overwork to compensate. It's a mess of anxiety and unease, and many of my non-White clients have enjoyed working from home during quarantine just to get some space from all that. It may make people denigrate their own race and admire the other, as in the expression "the White man's ice is cooler."

TCPR: What is interpersonal racism?

Dr. Cyrus: Interpersonal racism involves the ways people interact, and it's where microaggressions come in. Something offensive might be said to a person of color, or they may be ignored, passed over for promotions, or have their name constantly mispronounced. They may spend the whole day wondering, "Was that really directed toward me? Am I overreacting?" Neglect and omission are the interactions that particularly hurt.

TCPR: Are microaggressions different from trauma?

Dr. Cyrus: Microaggressions can be traumatic, but I think of them as little tiny cuts rather than a mortal wound like a trauma. It's hard to say what's "micro." When I'm called "sir" in public (and I am a woman), is that micro to me? If I were a transgender woman and someone called me "sir," how much would that hurt?

Continued on page 4

Expert Interview
Continued from page 3

TCPR: Trauma involves a threat to life or bodily integrity, while microaggressions seem to reinforce a marginalized status.
Dr. Cyrus: Yes. Microaggressions often remind people of bad experiences they've had in a racist society, and for some those bad experiences include traumas the way they are defined in DSM-5. Psychiatrists like to categorize and delineate things, but how do you categorize the concept of spending your whole life in a racist society? Is that an ongoing trauma?
TCPR: Should we screen for microaggressions?
Dr. Cyrus: It's a good idea. It conveys compassion. Ask, "Are there any social experiences that have been particularly traumatic and that you still think about?" "How have your identities impacted your experience?"
TCPR: How can we let the patient know we are on their side, even though we may blunder and fail to fully understand all they've been through?
Dr. Cyrus: Mistakes are inevitable. One strategy is to ask yourself, "What if I were someone from the opposite political party, someone from a different gender or race, or someone in a wheelchair?" Talk to people who are from different walks of life and learn from them. It's not just the words we use, but everything down to how we design our office space. Are we making people who are different from us feel welcomed? Or are the magazines and decor in our waiting room the kind of stuff that would mainly appeal to psychiatrists?
TCPR: How can we make our offices more inclusive?
Dr. Cyrus: Patients who are used to interacting with people who don't look like them are looking for clues that you're safe. It helps to develop a mental routine where you walk into a room and think, "Whom is this space *not* amenable to?" Where is your office located? What are the houses like around you? Will people of a different gender or race feel safe there at night? What kind of magazines do you have? Do you have a rainbow flag anywhere?
TCPR: How can we open up that conversation in the consulting room?
Dr. Cyrus: Ask, "Are there differences between us that you are worried about—that might affect our interactions or my ability to understand and help you?" Even though there is a mismatch in the supply of providers who might look like some of these people of color, you have to be able to talk about race right now (Miu AS and Moore JR, *Acad Psychiatry* 2021;45(5):539–544). You are not going to be able to do it perfectly. The first step is just knowing that you're going have to talk about it.
TCPR: Thank you for your time, Dr. Cyrus.

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How to Use Varenicline (Chantix)
Continued from page 1

The Pfizer patent had already expired a few months before this shutdown, and a generic varenicline is now on the market. With the price in decline and the appearance of new studies suggesting that this medication is safer than previously thought, it's a good time to reevaluate where varenicline fits in psychiatric practice.

Tobacco use has declined significantly since the 1960s, when close to 50% of the adult US population smoked cigarettes. Today that figure is closer to 14%, but the rates have not declined as much for people with mental illness, including substance use disorders, who now make up nearly half of all smokers. This is in part due to the worsening of anxiety and depression some patients experience when quitting, though these symptoms typically resolve within the first few weeks or the first month. On the other hand, quitting has significant long-term benefits for both physical and mental health (Taylor G et al, *BMJ* 2014;348:g1151).

Varenicline (Chantix) Facts	
FDA indications	Nicotine cessation
Other uses	Alcohol use disorders (when comorbid with nicotine)
Dosage	Start 0.5 mg QAM for three days then 0.5 mg BID for four days, then 1 mg BID
Side effects	Nausea, insomnia, nightmares
Interactions	None (renally excreted)
Contraindications	None
Cost	$350/month (a generic is expected soon)

How well does varenicline work?

Nicotine produces its rewarding effects by activating the nicotinic acetylcholine receptors, a third of which project to the mesolimbic dopamine region. There, the nucleus accumbens or "pleasure center" is activated. Varenicline is a selective partial agonist with high affinity for the α4β2 site on the nicotinic receptor. It blocks nicotine from binding to that site, but as a partial agonist it still activates the receptor enough to prevent withdrawal symptoms and reduce cravings (Jordan CJ and Xi ZX, *Expert Opin Drug Discov* 2018;13(7):671–683).

That sounds good in theory, but what about the clinical evidence? A meta-analysis of over 100 trials concluded that varenicline was just over twice as effective as nicotine replacement therapies and bupropion in helping patients quit (Mills EJ et al, *Harm Reduct J* 2009;6:25). That finding was further confirmed in psychiatric populations in a large, industry-sponsored trial (Anthenelli RM et al, *Lancet* 2016;387(10037):2507–2520).

If a patient does not respond to varenicline, combining it with a nicotine patch can enhance its efficacy, as was shown in a long-term randomized controlled trial (Chang PH et al, *BMC Public Health* 2015;15:689). Nicotine patches can be started at any time, but this study started them one week before

Continued on page 6

Tricyclic Antidepressants: When and How to Use Them

Edmund S. Higgins, MD. Clinical associate professor, Psychiatry and Behavioral Sciences, Medical University of South Carolina.

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

Tricyclics have been used in psychiatry since the 1950s, when imipramine was introduced as the first mass-marketed antidepressant. Fluoxetine and the other SSRIs largely supplanted the tricyclics in the 1990s, but these medications still have their uses.

There are two kinds of tricyclics:

1. Tertiary amines—the *"originals"*
2. Secondary amines—the *"metabolites"*

The tertiary amines are the oldest tricyclics and have norepinephrine as well as some serotonin reuptake inhibition, while their metabolites, the secondary amines, mainly inhibit norepinephrine reuptake.

When to use them

When all depressions are lumped together, the tricyclics are equally as effective as other antidepressants (Undurraga J and Baldessarini RJ, *J Psychopharmacol* 2017;31(9):1184–1189). However, tricyclics are potentially more effective for certain conditions:

- **Melancholic depression.** Melancholic depression is characterized by widespread loss of pleasure, ruminating guilt, loss of appetite, early morning awakening, and prominent psychomotor changes. Patients with this subtype of depression respond better to tricyclics than SSRIs (Undurraga J et al, *J Psychopharmacol* 2020;34(12):1355–1341).
- **Depression with chronic pain.** Tricyclics relieve neuropathic pain independently of their antidepressant effects. Their benefits in depression with comorbid pain are comparable to duloxetine's and superior to the SSRIs. In fibromyalgia, low-dose amitriptyline was more effective for insomnia and fatigue (25–50 mg QHS), while duloxetine showed more improvements with mood (de Farias AD et al, *Adv Rheumatol* 2020;60(1):35).
- **Depression with irritable bowel syndrome.** Tricyclics, particularly amitriptyline and imipramine, are more effective than SSRIs in irritable bowel syndrome (Xie C et al, *PLoS One* 2015;10(8):e0127815).
- **Prevention after ECT.** Many consider the combination of nortriptyline and lithium after ECT to be the gold standard for forestalling the return of depression (Sackeim HA et al, *JAMA* 2001;285(10):1299–1307).
- **OCD.** Clomipramine is the only tricyclic with good evidence in OCD, and it may be slightly more effective than the SSRIs (Sánchez-Meca J et al, *J Anxiety Disord* 2014;28(1):31–44).
- **Sexual side effects.** The secondary amines are less likely to cause anorgasmia but more likely to cause erectile dysfunction (Werneke U et al, *Acta Psychiatr Scand* 2006;114(6):384–397).

Antidepressant augmentation

Tricyclics have been used to augment other antidepressants, particularly the SSRIs, since the 1980s (Taylor D, *Br J Psychiatry* 1995;167(5):575–580). In theory, the tricyclics provide noradrenergic effects that enhance the antidepressant response, but this combination can also be dangerous due to a drug interaction in the hepatic CYP enzymes (Palaniyappan L et al, *Adv Psych Treatment* 2009;15(2):90–99). Many modern antidepressants raise tricyclic levels,* so start low and increase slowly. Nortriptyline is one of the better-studied tricyclics for augmentation, and its well-established serum levels make drug interactions easier to monitor.

**Exceptions include citalopram, escitalopram, desvenlafaxine, mirtazapine, trazodone, vilazodone, and vortioxetine.*

Risks and side effects

The tricyclics are best avoided in bipolar disorder as they rank near the top of antidepressants regarding their potential to induce mania and mixed states (Koszewska I and Rybakowski JK, *Neuropsychobiology* 2009;59(1):12–16). They are risky in borderline personality disorder as well, in part because they are toxic in overdose, and an amitriptyline study suggests they may trigger aggression and disinhibition in this population (Soloff PH et al, *Psychopharmacol Bull* 1987;23(1):177–181).

Caution is also warranted in patients with cardiac conduction disorders, as tricyclics have type 1 antiarrhythmic qualities. This risk is what makes them fatal in overdose, hence they are sometimes avoided or dispensed only in small quantities to actively suicidal patients.

Like most antidepressants, tricyclics can cause sedation, weight gain, and sexual dysfunction. These risks vary among the agents and are generally lower with the secondary amines. Outside of that, tricyclics' main side effects are as follows:

1. Anticholinergic (see table at bottom of page for management): Constipation, urinary retention, dry mouth, blurred vision, confusion
2. Cardiovascular: Orthostatic hypotension, falls, cardiac arrhythmias
3. Hepatotoxicity: Extremely rare (four per 100,000 patient-years)

You're more likely to see problems in the elderly with orthostatic falls and anticholinergic side effects. The latter may present as difficulty reading (from blurred vision), dental problems (from dry mouth), and—in more serious cases—small bowel obstruction from constipation or urinary tract infection from urine

Continued on page 7

Managing Tricyclic Side Effects

Constipation	Docusate 100 mg BID with sennosides 8.6 mg intermittently daily as needed; bethanechol 10–25 mg TID for severe cases
Dry mouth	Xylitol gum (eg, Spry) TID Biotene products Pilocarpine 4% drop solution (dilute by mixing one part med with three parts water; swish solution in mouth for one minute Q8hr PRN; do not swallow)
Orthostasis	Elastic abdominal binders or support stockings Oral fludrocortisone 0.1–0.2 mg QD or midodrine 5 mg TID
Urinary retention	Bethanechol 25 mg TID

How to Use Varenicline (Chantix)
Continued from page 4

starting varenicline. The combination did not add significantly to varenicline's side effects.

Many smokers use nicotine and alcohol together, with each one triggering the other. The nicotinic acetylcholine receptor (nAChR) is involved in modulating the rewarding effects of alcohol, and clinical evidence shows that varenicline reduces alcohol use in smokers who drink (Mitchell JM et al, *Psychopharmacology (Berl)* 2012;223(3):299–306).

Billing for Nicotine Cessation

Many insurers reimburse for nicotine cessation counseling. These codes can be added on to an E/M visit (for Medicare, use modifier -25 to indicate it is a separate service performed on the same day). Typical Medicare reimbursement rates are $15 for 99406 and $28 for 99407.

99406	Nicotine counseling 3–10 minutes
99407	Nicotine counseling >10 minutes
Documentation	Time spent and brief details of discussion (eg, "assessed motivation to quit," "provided skills and resources to quit," "set quit date," "discussed impact of smoking," "management of cravings and triggers")

Side effects

Varenicline's most frequent side effects are nausea and insomnia. When varenicline is titrated up slowly, the incidence of nausea is reduced to about 15% of patients. About one in three patients have insomnia on the drug, which usually subsides after the first month. Other side effects include abnormal dreams, headache, dizziness, and constipation. Nightmares are the most troubling of these and may improve with clonidine (0.1–0.2 mg). In addition to reducing nightmares, clonidine may reduce nicotine cravings and withdrawal symptoms (Cahill K et al, *Cochrane Database Syst Rev* 2013;2013(5):CD009329).

Varenicline's neuropsychiatric side effects have been more controversial. In 2009, the FDA placed a black box warning on varenicline that noted its potential to cause depressed mood, suicidal ideation and attempts, agitation, psychosis, and accidental injuries including traffic accidents. That was followed in 2015 by a new warning that varenicline may reduce alcohol tolerance, raising the risk of blackouts and seizures.

Those warnings were downgraded in 2016 following two important reviews. The first, a meta-analysis of over 10,000 smokers, found no clear relationship between taking varenicline and the development of depression, agitation, or suicidal ideation (Thomas KH et al, *BMJ* 2015;350:h1109). This was followed by a randomized, double-blind, controlled international study of over 8,000 participants, half with and half without a previous psychiatric history. The study, which was industry sponsored, showed no significant increase in moderate to severe neuropsychiatric events (Anthenelli RM et al, *Lancet* 2016; 387 (10037):2507–2520). While these newer data are reassuring, most psychotropics have the potential to cause rare neuropsychiatric problems, and I wouldn't rule this possibility out for varenicline.

On the medical side, there were concerns about heart attacks and stroke on varenicline, but the FDA was reassured after a large randomized controlled trial did not find a statistical increase in these events (Benowitz NL et al, *JAMA Intern Med* 2018;178(5):622–631).

How to prescribe varenicline

The most difficult part of prescribing varenicline is engaging the patient's motivation. Most patients want to quit smoking at some point in their lives. With this in mind, I keep nicotine dependence on the problem list and repeatedly let the patient know I will support their attempt to quit when they're ready and have tools that may help them succeed at doing so. When the patient is ready, help them establish a workable quit date, ideally a day when support is available and they've made behavioral changes to distract them from cravings.

Start varenicline seven days prior to the quit date as described in the table on page 4. When prescribing, I'll say to the patient: "Remember, you may still have some symptoms of nicotine withdrawal, most commonly agitation, but they are reduced when taking this medication. The most common side effect is nausea, which we'll try to avoid by raising the dose slowly. I am delighted you are taking this big step in caring for yourself. I know it's not easy. Let me know if there are problems."

Patients should continue varenicline for at least three months after quitting. I usually continue it as long as the patient feels it is helping.

Like all anti-addiction agents, varenicline works best when used with relapse prevention counseling. As the patient is attempting to quit, I encourage behavioral changes such as putting their cigarettes out of reach, moving the chair they often smoke in, or cleaning their ashtray right after smoking. These changes and others cut down on triggers and lower the potential of unconsciously lighting up. I always encourage patients to contact QuitLine (1-800-QUIT-NOW), which is available in every state and paid for by cigarette taxes.

Henry decides to start varenicline and is able to gradually quit smoking, lowering to six cigarettes a day after a week and then quitting completely after three weeks on the drug. He engages with QuitLine and reduces his triggers, one of which is alcohol. Like many smokers, he finds it easier to maintain his reduction in drinking while on varenicline.

CARLAT VERDICT

Ask patients regularly about nicotine use and use a counseling approach when prescribing medication for smoking cessation. When it comes to efficacy, varenicline has an edge over other medications. In terms of side effects, it looks like the risks have been overstated, and people with psychiatric illness tolerate varenicline just as well as those without.

CME Post-Test

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1. Compared to SSRIs, tricyclics are more effective in which condition(s) (LO #2)?
   - [ ] a. Borderline personality disorder
   - [ ] b. Melancholic depression
   - [ ] c. Bipolar disorder
   - [ ] d. Tricyclics are not more effective than SSRIs in any psychiatric condition

2. Recent studies indicate that varenicline is associated with an increased risk of depression, agitation, suicidal ideation, heart attack, and stroke (LO #1).
   - [ ] a. True
   - [ ] b. False

3. According to Dr. Cyrus, which of the following terms most closely represents a form of self-hatred that can take varying levels of intensity, like feeling embarrassed, ashamed, or angry in association with one's race (LO #3)?
   - [ ] a. Internalized racism
   - [ ] b. Interpersonal racism
   - [ ] c. Systemic racism
   - [ ] d. Microaggression

4. What have recent studies concluded about the efficacy of varenicline for nicotine dependence (LO #1)?
   - [ ] a. Varenicline is a full agonist of the nicotinic acetylcholine receptor, and it does not prevent or reduce cravings
   - [ ] b. Varenicline is about twice as effective as nicotine replacement therapies and bupropion for smoking cessation
   - [ ] c. Varenicline's efficacy can be enhanced when combined with a nicotine patch, but combination treatment significantly worsens varenicline's side effects
   - [ ] d. Varenicline reduces nicotine use but has no effect on alcohol use

5. Which tricyclic is best for those at risk for falls and, when combined with lithium, is considered the gold standard for preventing depression relapse after ECT (LO #2)?
   - [ ] a. Imipramine
   - [ ] b. Amitriptyline
   - [ ] c. Doxepin
   - [ ] d. Nortriptyline

Tricyclic Antidepressants: When and How to Use Them

Continued from page 5

retention. Anticholinergics can also cause confusion and may increase the risk of dementia (Coupland CA et al, *JAMA Inter Med* 2019;179(8):1084–1093). Among the tricyclics, amitriptyline is the most anticholinergic, while nortriptyline and desipramine are the least.

Which to start with?

It is usually best to start with a secondary amine due to their higher tolerability. However, each tricyclic has unique properties that may make it the right fit for your patient. Clomipramine is best for OCD, doxepin for insomnia, and nortriptyline for those at risk of falls (see table at right).

Dosing

As with most antidepressants, slow titration of tricyclics improves tolerability, such as raising the dose every five

Continued on page 8

Tricyclic Antidepressants

	Medication	Unique Features	Dosing
Tertiary Amines	Amitriptyline	Highest anticholinergic burden, high sedation	Start 25–50 mg QHS, target 150–300 mg/day
	Clomipramine	Best for OCD, most serotonergic	Start 25 mg/day, target 150–250 mg/day
	Doxepin	Most sedating and antihistaminergic	Start 25–75 mg QHS, target 150–300 mg/day (for insomnia, 3–6 mg HS)
	Imipramine	Best studied for panic disorder and anxious depression	Start 25–50 mg/day, target 150–300 mg/day
Secondary Amines	Desipramine	Strongest norepinephrine effects, lowest anticholinergic burden, low risk of sedation	Start 25–50 mg/day, target 75–300 mg/day
	Nortriptyline	Lowest risk of orthostasis and weight gain; in combination with lithium is a good strategy to maintain recovery after ECT	Start 25–50 mg/day, target 50–150 mg/day
	Protriptyline	Least sedating and may be activating	Start 5–10 mg/day, target 15–60 mg/day

Sources: Goldberg JF and Stahl SM, Practical Pharmacology, *2021;* Kaplan & Sadock's Comprehensive Textbook of Psychiatry, *2017.*

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Tricyclic Antidepressants: When and How to Use Them

Continued from page 7

to seven days. Only three of the tricyclics have fairly reliable serum levels that can guide treatment: nortriptyline, imipramine plus its metabolite desipramine, and desipramine by itself. One caveat: These serum levels are most relevant to melancholic depression, which is the population in which most of the research was conducted. Nortriptyline's ideal serum level (the best studied of the three) forms an upside-down "U-shaped" curve, meaning it's less effective if too low or too high—a level between 50 and 150 ng/mL is the sweet spot. For imipramine, the best level is over 200 ng/mL (this value includes its active metabolite desipramine, sometimes called desmethylimipramine). Levels over 250 ng/mL were no more effective in studies but resulted in more side effects. Desipramine serum levels over 125 ng/mL can improve outcomes. Check serum levels eight to 12 hours after the last dose, and at least five half-lives (five to six days) after reaching the full dose.

CARLAT VERDICT

Tricyclics are rarely first line, but they are a good option in select situations, such as melancholic and treatment-resistant depression, depression with chronic pain, and OCD. With careful management and judicious selection, they are often better tolerated than their reputation suggests.

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