



July 2022

More on varenicline

Murray et al have written a timely, thoughtful, and useful article (“Smoking cessation: Varenicline and the risk of neuropsychiatric adverse events,” *CURRENT PSYCHIATRY*, July 2022, p. 41-45) about the role of the nicotinic acetylcholine receptor partial agonist varenicline for helping patients stop smoking, which is still the main preventable cause of morbidity and premature death. Smoking remains a major problem among patients who are chronically mentally ill and those with substance use disorders, as well as “recovering” populations such as Alcoholic Anonymous participants.¹ Reviews of the EAGLES trial and other research analyses have gone a long way to allaying anxiety about interventions for smoking cessation.²

Just a few caveats regarding Murray et al’s excellent summary:

- The article did not address that nicotine is consumed in multiple ways, such as vaping, snuff, chewing tobacco, and hookah
- The safety of varenicline appears fair when psychiatric illness is well controlled but can be problematic (and even severely detrimental) when mental illness is not well controlled. This should not be glossed over,

especially since it was the reason for the original black-box warning (for risks including behavioral impulsivity, suicidality, severe insomnia, and nightmares) that was removed in 2016

- Patients with severe mental illness may not fully understand the risks, benefits, and priorities of the treatment intervention. The importance of psychiatric and internal medicine in addition to pharmacy follow-up is critical and needs to be documented.

Varenicline has been contextualized in its current role as a first-line treatment for smoking cessation. By bypassing a sizeable population of patients who have unstable psychiatric illness (especially bipolar I disorder), the path has been opened for risky “off-label” varenicline prescribing to this population by inter-nists, who should be very cautious and prudent about prescribing for such patients. This alone is probably a good reason to reinstate the black-box warning.

Interestingly, one review found that only 1 of 11 patients receiving varenicline stopped smoking.¹ Not dramatically beneficial for a first-line treatment! Decreasing smoking occurs as well and is more robust with combinational use with bupropion, nicotine replacement therapy, and cognitive-behavioral therapy.

If we are focusing on patients with unstable mental illness—who are seen primarily by psychiatrists—adherence, urgency of intervention, and context regarding acute safety for this population must be seen as top priorities.

So-called “second-line” treatment options must also be considered. Sandiego et al³ make excellent

points regarding the role of alpha-adrenergic agonists such as guanfacine, which have been shown to be helpful in smoking cessation. They work by decreasing cortical dopamine release and their calming effects on the noradrenergic system, which may decrease smoking precipitated by stress. For the particularly challenging subpopulation of unstable smokers, the combination of varenicline plus guanfacine ER may turn out to be a game-changer.

Varenicline has not proven itself to be useful in patients who are severely mentally ill, and due to its low success rate, expectations should remain tempered, pragmatically realistic, and safety-based.^{4,5} The bottom line is that in an unstable psychiatrically ill patient, interventions other than varenicline should be first-line.

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Disclosures

The author reports no financial relationships with any companies whose products are mentioned in his letter, or with manufacturers of competing products.

doi: 10.12788/cp.0299

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