

### Vigilance needed with methamphetamine-associated psychosis

We thank Drs. Palis and MacDonald for their commentary on incorporating prescription psychostimulants into the continuum of care for people with stimulant use disorder.<sup>1</sup> Although the evidence is still evolving, psychostimulants remain promising agents for the pharmacologic treatment of stimulant use disorder. However, the article raises some issues that warrant further discussion, particularly concerning treating patients with important psychiatric comorbidities.

Palis and MacDonald cite a meta-analysis by Tardelli and colleagues, which concludes that psychostimulants are a safe and effective treatment for stimulant use disorder.<sup>2</sup> However, stimulant use disorder is a broad category, and the outcomes described in people with cocaine use disorder and methamphetamine use disorder differ. Although the potential for effectiveness in treating methamphetamine use disorder is not excluded, the findings by Tardelli and colleagues primarily stem from studies focusing on cocaine use disorder, and the generalizability of those results to methamphetamine use disorder remains unclear.

Although Palis and MacDonald characterize psychostimulants among people with stimulant use disorder as “not associated with adverse events,” available studies involving a general population have shown that psychostimulants appear to carry a risk of psychosis. A large registry study established a baseline risk for inducing psychosis of about 1 in 660.<sup>3</sup> This risk may be small but is increased for those who have previously developed psychosis after a prescription. Cressman and colleagues found that reinitiating psychostimulant treatment led to hospital readmission in 45% of individuals previously admitted for mania or psychosis associated with psychostimulants.<sup>4</sup>

This risk is particularly relevant considering that psychosis can be a sequela of both methamphetamine use disorder and psychostimulants, and the authors have

highlighted that 40% of people who use unregulated methamphetamines experience methamphetamine-associated psychosis. Unfortunately, psychostimulant trials typically regard the presence or history of psychosis as an exclusion criterion, thus limiting any safety conclusions for this population. By stating that prescription psychostimulants have a lower rate of inducing psychosis, Palis and MacDonald imply that the practice protects against psychosis. However, as psychostimulants have not been shown definitively to be safe in this population nor consistently found to reduce methamphetamine use, they cannot be automatically expected to reduce the risk for psychosis. Notably, a Danish registry study indicates that the conversion of methamphetamine-associated psychosis to schizophrenia occurs in 20.2%,<sup>5</sup> which underscores the need for extreme vigilance among patients who have experienced this type of psychosis.

A salient question remains unanswered: how much risk do psychostimulants pose for inducing psychosis in those with previous methamphetamine-associated psychosis? For now, the uncertainty surrounding this clinical issue calls for caution rather than confidence. Although we agree that there is an increasing role for using psychostimulants in treating methamphetamine use disorder, the clinical work of reducing harm and balancing multiple layers of harm continues to be challenging.

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