Microscopes and Telescopes: the Societal Impact of Substance Use Disorder Treatment

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Clinical trials are designed to tell us whether a particular treatment for a specific disorder is efficacious. Yet even a large clinical trial is insufficient to predict the population-level public health impact of that treatment as well as the individual-level likelihood of treatment outcome success. Clinical trials in behavioral health are typically of short-term duration, often lasting 3–6 months. This duration does not adequately reflect the societal impact of certain disorders, in this case substance use disorders, in which relevant outcomes reflecting mortality (e.g., overdose, deaths by suicide, substance-related fatal injury) and other costs to society (e.g., criminal activity, employment disability, health care costs, and impact on families) generally occur episodically over time and may not manifest during the course of a short-term trial. Moreover, some clinical trials, particularly early-stage trials designed to facilitate attainment of regulatory approval of a medication, exclude patients with co-occurring psychopathology and other social determinants of health (e.g., inadequate housing and transportation barriers) that significantly affect individual and social outcomes.

As an example, we have learned from randomized clinical trials that naltrexone and acamprosate are moderately efficacious treatments for alcohol use disorder and that buprenorphine, extended-release naltrexone, and methadone are robustly efficacious treatments for opioid use disorder. To learn more about the public health impact of using these medications in practice, we must shift lenses, and for this perspective a study using population-based registry data of naturalistic clinical practice is ideal. One might consider a randomized controlled clinical trial as examining a public health problem through the lens of a microscope, seeking cause and effect of an applied treatment in ameliorating that problem, while a registry study is analogous to viewing the same public health problem through a telescope, investigating the broader impact of that same applied treatment in large and diverse populations.

In this issue of the *Journal*, Molero and her collaborators (1) at the Karolinska Institute have done just that. Using data from Swedish population-based registries between 2005 and 2013, they conducted a total population cohort study in which they examined people who had taken either acamprosate or oral naltrexone for alcohol use disorder or had taken buprenorphine or methadone for opioid use disorder (total N=21,281), and compared their rates of suicidal behavior (defined as either suicide attempt or completion), unintentional substance overdose, and criminal activity during periods when they were medication adherent with periods in which they were not prescribed or not taking medication. The study was elegantly conducted, with careful attention to issues such as reverse causality (i.e., whether medications were prescribed in reaction to an outcome of interest), the possibility that other medication use (e.g., antidepressants and benzodiazepines) could have influenced the outcomes, and whether nonspecific effects of encounters with the health care system may have affected the results.

The authors report that naltrexone was associated with fewer substance-related accidental overdoses, whereas the other alcohol use disorder medication, acamprosate, was not associated with any of the outcomes of interest (note that in Sweden, naltrexone is approved for the treatment of alcohol use disorder but not opioid use disorder). Patients taking either naltrexone or acamprosate and also taking a benzodiazepine had increased suicidal behaviors. Buprenorphine for opioid use disorder was associated with a lower risk of substance-related accidental overdose as well as a reduction in a wide variety of criminal behaviors: violent, nonviolent, and substance-related crimes. Methadone for opioid use disorder was associated with a reduction in all categories of crime as well as reduced suicidal behaviors, yet it was associated with an increase in substance-related accidental overdoses, presumably due to its opioidergic potency and synergy with other substances (e.g., benzodiazepines) that reduce respiratory functioning or add risk for cardiac arrhythmia.

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This study adds important data to the conversations currently under way in the United States around health care for substance use disorders, mainly on several points regarding effective services for substance use disorder treatment and secondary or tertiary prevention. In the United States, alcohol use disorder, especially binge drinking, remains the highest-prevalence preventable substance-related

health problem, alongside tobacco-related health problems, with approximately 1 in 4 adults reporting binge drinking in the past 30 days (defined as ≥4 standard drinks per episode for women and ≥5 for men) and 1 in 10 adults meeting criteria for chronic alcohol use disorder (2). Both naltrexone and acamprosate are recommended for the treatment of alcohol use disorder in community care (3), yet the Molero et al. study, coupled with the results from the multisite National Institute on Alcohol Abuse and Alcoholism COMBINE trial (4), in which acamprosate did not perform superiorly to placebo but naltrexone and evidence-based psychotherapy did, suggest a preference for naltrexone as a first-line option for individuals with adequate hepatic functioning (acamprosate is renally cleared and therefore may be safer for patients with clinically significant hepatic dysfunction related to alcohol use or other causes). It is also noteworthy that adjunctive benzodiazepine therapy was observed to increase risk for suicidal behaviors among these patients, given the common prescribing of concurrent benzodiazepine therapy to address symptoms associated with alcohol use disorder, such as acute withdrawal syndromes and co-occurring anxiety or insomnia in early abstinence. Recent studies highlight the potential negative outcomes of benzodiazepine prescribing in the context of treatment for opioid use disorder (5), but none before the Molero et al. study have specifically examined its proximal relationship to negative outcomes during longer-term treatment of alcohol use disorder. An examination of this in U.S. cohorts would provide an important replication study.

Opioid use disorder has been extensively studied in the United States for protective outcomes associated with both buprenorphine and methadone, particularly with respect to reductions in crime, infectious disease transmission, and substance-related overdose while in treatment (6). More recently, focus on suicide prevention in opioid use disorder has been elevated, since national estimates suggest that 10%−30% of overdose deaths coded as "unintentional" or "undetermined" are misclassified suicides (7, 8). From this perspective, one could take two differing views on self-injury mortality prevention in opioid use disorder. One perspective would be to pose that both buprenorphine and methadone prevent self-injury mortality (i.e., both intentional and unintentional overdose deaths) by virtue of examining global reductions in overdose deaths during active treatment, given the uncertainty of precisely defining intent at the time of overdose behavior. The study by Molero et al. would support this public health approach in using either medication. An alternative perspective would be to stratify the population according to risk factors associated with elevated probability of suicidal behaviors that present additive risk for opioid-related mortality. From this perspective, the additional suicide prevention effects observed with methadone in this study, compared with buprenorphine, may be significant and worth further clarifying in order to improve reduced mortality in subpopulations of patients with opioid use disorder who have greater suicide risk factors, such as childhood trauma and mental health disorders. Interestingly, studies of the acute effects of buprenorphine in reducing treatment-resistant depression symptoms and suicidal ideation among patients without substance use disorders (9, 10) have encouraged U.S. clinicians to consider buprenorphine as potentially superior to methadone in preventing suicidal behaviors, potentially biasing prescribing behavior in the United States in ways inconsistent with the outcomes observed in this study. The importance of using all our scientific lenses to improve secondary and tertiary prevention in behavioral health cannot be underestimated and is necessary for correct knowledge guiding primary prevention.

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