COMMENTARY

Do We Know Enough to Prescribe Opioid-Agonist Therapies to Adolescents With Problematic Opioid Use? A Commentary on Camenga et al. (2019)

CAMENGA AND COLLEAGUES (2019—this issue) carefully review the risks and benefits of prescribing U.S. Food and Drug Administration–approved medications to treat opioid use disorder (OUD) in adolescents. The evidence is extremely limited, derived from small samples or subsamples of patients enrolled in a modest number of studies. This reflects a widespread problem within the field: Although addiction typically begins in adolescence, adults overwhelmingly comprise treatment research samples (U.S. Department of Health and Human Services, 2016). Because we suspect clinical concern and interest in this area will center more on opioid-agonist therapies than on naltrexone, we focus this commentary on the former, beyond noting that we agree with Camenga and colleagues’ analysis of naltrexone. On the principle of *primum non nocere*, we describe here three potential risks of opioid-agonist therapies in adolescents about which we have almost no data.

First, methadone was developed and its associated clinical practices devised to effectively treat adults with long-term OUD (primary heroin use disorder; Kreek, 2000; Strang et al., 2012). Camenga and colleagues mention correctly that dosages derived from adults may not apply to adolescents, but translational concerns go beyond that important issue. From a health care prescriber’s perspective, initiating methadone maintenance with a 16-year-old is fundamentally different than doing so with, for example, a 40-year-old, because only the former may end up taking the medication for a half century or more. Although the risks associated with illicit opioid use are usually more significant acutely, other risks we may not yet understand could arise from taking an opioid-agonist medication for such a long time, particularly when it begins during the period of high neuroplasticity characteristic of the adolescent brain.

Second, the evidence in support of opioid-substitution medication that Camenga and colleagues review comes mainly in the form of treatment retention data. Opioid-substitution therapies tend to have better-than-average retention because of the reinforcing effect of the medication. Retention is necessary for good treatment outcomes but cannot be equated with them. Daubresse and colleagues (2017) recently documented that more than two fifths of

buprenorphine-maintained patients continue to consume prescription opioids during treatment, and other studies suggest that drinking problems are prevalent among opioid-maintained patients and may even increase over time (Hall & Strang, 2017). When we turn our attention to actual clinical outcomes rather than just retention, the available evidence for opioid-agonist medications in adolescents is weaker. As noted by Camenga et al., although some short-term drops in illicit opioid use have been found in buprenorphine trials, only one study has assessed outcome even as far out as 12 weeks, and that trial showed no effect on illicit drug use. Direct data on illicit opioid and other substance use outcomes are desperately needed for adolescents on opioid-agonist therapy, as are data on quality of life, family bonding, and educational engagement/attainment.

Third, particular care must be taken with this age group to assure that the adolescent is truly dependent on opioids before prescribing methadone or buprenorphine. It is not hard to correctly diagnose the dependence of a 65-year-old who has been injecting heroin for decades. But it can be challenging to determine whether 16-year-olds are truly dependent on Vicodin if they have been frequenting parties in which they are among many teenagers who consume the drug. If not, and the misuse of opioids is primarily a behavioral issue, then long-term opioid-agonist therapy could have adverse consequences. Adolescence is a time of high neuroplasticity (Crews et al., 2007), and if a child is not truly opioid dependent, then treatment could instill dependence where it did not exist before. Careful diagnosis by experts on adolescent opioid use disorder will be necessary to protect against this potentially harmful outcome.

Given that clinicians lack solid evidence to guide them, the debate about whether to prescribe opioid agonists to adolescents will be as much philosophical as empirical: How should we make treatment decisions when lives are at stake but the available data are not very clear? Camenga and colleagues suggest that even with imperfect information, medication-assisted treatment should be more widely considered for adolescent populations because of the known risks of untreated opioid use disorder. There are cases where almost everyone would agree that the balance of risks and

benefits for prescribing are easily appraised against this standard, either in favor of prescribing (e.g., an 18-year-old who has been regularly injecting heroin for 5 years and has had multiple ineffective prior treatments) or against it (e.g., a 12-year-old who misused his parents' pain medication out of curiosity). But most cases will be in between those poles, and frustratingly we do not know where to draw line in the sand. We read the limited evidence on opioid-agonist therapies a bit more cautiously than Camenga and colleagues, because of the risks unique to adolescents we have raised in this commentary and also because of the still slight knowledge scientists possess regarding adolescent brain development. But we agree with them wholeheartedly that this area merits expanded, urgent, scientific attention so that clinicians can better judge the risks and benefits of pharmacotherapy for adolescents with OUD.

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