Medical Treatment of Opiate Dependence: Expanding Treatment Options

This issue of the *Journal* contains an article by Kakko and colleagues describing the comparison of a stepped care strategy using buprenorphine and methadone maintenance therapy versus standard methadone maintenance therapy in heroin-dependent individuals. In this controlled trial, individuals randomly assigned to the stepped care arm all initiated treatment with a buprenorphine-naltrexone combination drug. Those who continued to experience symptoms of opiate withdrawal or other signs of inadequate clinical response while taking the maximum allowable dose of buprenorphine-naltrexone were switched to methadone. There were a number of interesting findings. Using retention in treatment as the primary a priori outcome measure, the investigators found no difference between groups. For both stepped care and standard methadone maintenance therapy, overall 6-month retention was 78%. However, among the stepped care completers, only 46% (17 of 38) continued to take buprenorphine-naltrexone, and 54% (20 of 38) were switched to methadone. In both groups, the proportion of urine samples free of opiates increased over time, and problems related to drug use decreased over time.

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This study is important in several ways. The use of maintenance medications in the treatment of opiate dependence clearly improves treatment outcomes, and the most recent National Institutes of Health consensus statement on this issue states that all persons dependent on opiates should have access to medication maintenance therapy under proper supervision. However, methadone use is highly restricted and only available for the treatment of opiate dependence at specialized clinics. Barriers to patients entering licensed opioid treatment programs include state and federal regulations for program admittance, treatment costs, and limited expansion of treatment centers since the 1980s. The social stigma associated with methadone treatment may also play a role in discouraging opioid-dependent individuals from entering treatment. In 2005, approximately 250,000 of the 2 million current, long-term opioid users in the United States were receiving methadone. Buprenorphine, a semisynthetic opioid, is a mixed agonist/antagonist at the μ opioid receptor. Because of its partial agonist properties, there is a decreased risk of overdose as compared to methadone. Because of extensive metabolism by the intestine and liver, buprenorphine is poorly absorbed by the oral route and is therefore best administered by intravenous or sublingual dosing. The formulation is a buprenorphine-naltrexone combination designed for sublingual use to prevent diversion of buprenorphine for intravenous use. When taken sublingually, the naltrexone is largely unabsorbed and does not block the μ agonist effects. However, if this formulation is used intravenously, the naltrexone will precipitate withdrawal by blockade of μ opioid receptors. Another advantage of buprenorphine is the relatively long dose duration, which may allow for dosing every 2 to 3 days, as tolerated, compared to the daily dosing generally required for methadone.

The Drug Addiction Treatment Act of 2000 expanded the clinical context of medication-assisted treatment of opioid dependence by allowing qualified physicians to pre-

scribe buprenorphine for the treatment of opioid dependence in office-based settings. As initially approved, physicians were limited to the treatment of 30 patients at one time with buprenorphine. In the 2006 reauthorization of the Drug Addiction Treatment Act of 2000, this limit was increased to 100 patients per qualified physician. This is the first time in modern medicine that physicians in the United States practicing in a variety of clinical settings, including office-based practice, were able to adequately treat opioid dependence with pharmacotherapy. It is hoped that this will greatly increase access to treatment for opioid-dependent individuals and consequently decrease morbidity and mortality.

As the pharmacologic treatment options for opiate dependence expand, questions concerning the appropriate choice of agents for specific patients emerge. Although the advantages of buprenorphine in terms of safety and less restrictive outpatient treatment are clear, the comparative efficacy of methadone and buprenorphine remains an issue. Some studies suggest that buprenorphine is less efficacious than methadone in the treatment of opiate-dependent individuals (1–2). Adaptive approaches to the investigation of pharmacotherapeutic options have been used in other areas of psychiatry (3) and can provide valuable information to guide clinical practice. The well-designed, well-controlled study by Kakko and colleagues suggests that a substantial number of heroin-dependent individuals can be treated successfully with buprenorphine-naltrexone and raises the question of whether a trial of buprenorphine-naltrexone should be considered as a first step for opiate-dependent patients being considered for medical maintenance therapy. However, more than 50% of the subjects who were given buprenorphine-naltrexone were switched to methadone because of suboptimal response. Unfortunately, none of the variables investigated (gender, age, severity or duration of dependence) predicted the individuals who were switched to methadone. Thus, the study implies that existing methadone programs could adopt a stepped approach to medication maintenance and successfully maintain a significant proportion of patients taking buprenorphine-naltrexone but does not help in determining who those patients might be.

There are a number of issues that limit the usefulness of the study by Kakko et al. in informing clinical practice. The relatively high intensity of the psychosocial treatment is unlikely to mirror what is seen in general practice. In addition, the stepped methadone rescue and methadone switch feature of the study design require delivery in a setting similar to that of methadone maintenance. Thus, one of the main benefits of buprenorphine treatment—the fact that it can be delivered in a less restrictive outpatient setting—was negated. In addition, the study included only intravenous heroin users with an average duration of use of approximately 10 years. Buprenorphine may have more utility in prescription opiate-dependent individuals, individuals who are employed, and those who have not previously been receiving methadone maintenance therapy. For these individuals, the benefit of the less-restrictive outpatient treatment, prescriptions for take-home doses, and avoidance of the stigma of going to a methadone clinic may be critical factors in determining treatment retention and success. Future studies using a broader base of patients and a more generalizable office-based approach to treatment are necessary to help clinicians and patients gain from some of the unique benefits of buprenorphine treatment. We commend Kakko and colleagues for this well-designed study exploring an adaptive approach to the treatment of addictions. We hope that this will pave the way for future studies in opiate dependence and other addictive disorders.

References

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