Data Do Not Support Buprenorphine as a First-Line Treatment for Addiction

TO THE EDITOR: In the May 2007 issue of the *Journal*, Johan Kakko, M.D., et al. reported on an excellent randomized controlled trial of "stepped" buprenorphine versus methadone therapy for heroin dependence (1). However, nearly two-thirds (65%) of the subjects were transferred to methadone because of continuing illicit drug consumption or cravings. Therefore, this study suggests that methadone should be the drug of first choice for maintenance treatment, and buprenorphine should be reserved for patients who do not respond well to methadone.

Most trials to date have reported that methadone provides superior retention (2). Methadone is also less expensive and easier and faster to administer than buprenorphine and is accepted as a safe treatment during pregnancy.

Dr. Kakko et al. reported a nonsignificant difference in their primary outcome of 6-month treatment retention, with 77% for buprenorphine and 79% for methadone. Such high retention is unusual for trials of this kind. In addition, the high buprenorphine retention may have been partly achieved by a more rapid dose escalation and a higher mean dose (29 mg/day) than usual.

Before the findings of Dr. Kakko et al. are accepted, there should be confirmation of the "noninferiority" of a standardized buprenorphine regimen in a community rather than clinic setting.

Methadone is more toxic than buprenorphine. This finding may not have been apparent in the study conducted by Dr. Kakko et al., since most of their patients ultimately received methadone. In some jurisdictions, buprenorphine is already the most frequently prescribed maintenance therapy for opioid addiction. It is undoubtedly an excellent second-line treatment.

Another important finding in this study was the average dose of 29 mg/day, which is more than double the average in most other studies and almost the manufacturer's maximum recommendation of 32 mg/day. Such a large dose often takes more than 15 minutes to administer. Dr. Kakko et al. speculated that the inclusion of naloxone (not naltrexone as stated in the editorial accompanying the article) in the combination product may have contributed to the need for such an unusually high dose. Other studies have reported higher doses required for the buprenorphine-naloxone combination (3). However, we are not aware of any rigorous "equivalence" studies comparing buprenorphine with the combination product.

The recommendation by Dr. Kakko et al. that buprenorphine should be considered as the first-line medication, despite 65% of patients being transferred to methadone, is difficult to accept. While industry support is often integral to the development of new intervention strategies, it has also been shown that studies funded by the pharmaceutical industry have a greater likelihood of reporting favorable conclusions (4).

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Dr. Byrne owns and runs a private clinic that dispenses methadone, buprenorphine, and other drug treatment. Dr. Wodak is the director of a public clinic (free to patients and government funded) that dispenses both methadone and buprenorphine.

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Dr. Heilig Replies

TO THE EDITOR: Buprenorphine and methadone are both effective treatments for heroin dependence (1). Counting studies on these medications is obviously not a valid method for comparing their efficacy. For retention in treatment, a meta-analysis yielded only a tendency-level advantage for methadone in high-dose studies (relative risk=0.79; 95% confidence interval [CI]=0.62–1.01) (1). In flexible-dose studies, the relative risk was similar, but reached significance (relative risk=0.82; 95% CI=0.69–0.96). For drug use and criminality, the two treatments were reported to be equivalent. Thus, methadone provides a slight advantage over buprenorphine for retention in treatment, and the two medications are equivalent on other relevant outcomes.

Methadone treatment is essential, but also has distinct limitations. As pointed out by Drs. Byrne and Wodak, methadone is "more toxic," i.e., methadone has sufficient mu-opioid receptor activity to induce lethal respiratory suppression, whereas buprenorphine, a partial agonist, does not. Safety itself aside, the monitoring necessitated by methadone use somewhat detracts focus away from building a therapeutic alliance, which offsets the cost advantage of the medication.

Given the complementary profiles of the two medications, pitching one against the other is not meaningful. The field needs rational ways of using both. In this context, we are unaware of any other therapeutic area in which a safer, albeit somewhat less effective medication, would be reserved for second-line treatment. Optimal balance between efficacy and safety is typically achieved by doing exactly the opposite. For example, few would consider using chloramphenicol for an infection before trying penicillin.

But what if stepping up treatment as needed rather than giving everyone methadone right away led to losing more patients overall? That would indeed mean that the safety gains

must be carefully weighed against efficacy losses, an exceedingly difficult tradeoff. Our study was designed to assess whether this is a concern and clearly showed that it is not. Nothing is lost by first trying the safer medication.

In that perspective, the exact proportion of patients who ultimately transfer to methadone is irrelevant. But let us be correct. In our study, among 48 subjects randomly assigned to stepped treatment, 37 remained. Of those, 20 transferred to methadone. That is 54%, which is what we reported. The 65% given by Drs. Byrne and Wodak is a misrepresentation of our data.

In summary, excellent outcomes can be achieved by starting every heroin-dependent patient with buprenorphine and progressing to methadone only if needed. These outcomes are as good as those achieved with the best possible methadone treatment. Among unselected individuals addicted to heroin who are retained in treatment, close to one-half do well without progressing to methadone. Each of these individuals represents a safety gain worth capturing.

Finally, our study disclosed an unrestricted research grant from industry that accounted for approximately 25% of the budget. The remaining funding came from the Swedish Government and Stockholm County. It is unclear how this could invalidate our results. The reference cited (2) by Drs. Byrne and Wodak in support of this notion deals with meta-analyses, which our study clearly is not.

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Suicide Deaths Concentrated in Beijing Universities

TO THE EDITOR: Earlier this year, five suicide deaths occurred among Beijing University students in only 8 days. Ironically, these events coincided with statements made by an official of China's Ministry of Education regarding the relatively low rate of suicide among university students in China. This official statement occurred at approximately the same time that a number of these suicide cases, as indicated below, were reported by the mainstream media.

On May 8, 2007 in Beijing, a female sophomore died from jumping from an academic building of her school at Beijing Petroleum University. On May 14th, a female junior from the Department of Architecture of Tsinghua University jumped from a school building and died at the scene. In the evening of the same day, a male student jumped from a building on the campus of the China Agriculture University. In each of the cases, the police confirmed the cause of death as suicide. On May 15th, a female graduate student at Beijing Normal University jumped from the 11th floor of a campus building and died at the scene. Preliminary cause of her death was determined as suicide as well (1).

The suicide deaths noted here occurred just prior to a statement on May 16th by the Chief of the Department of Ethics Education of China's Ministry of Education, which claimed that compared with the country's overall suicide rate of 23 per 100,000, the rate among university students is low, only 15 of the deaths among Beijing's 800,000 students (2).

In China, current university students are mostly born after the late 1970s, when the "One-Child" policy switched from being promoted to a mandatory status. Consequently, the majority of the current college-age population is comprised of young adults from single-child families. Hence, they are a population that has been a source of discussion regarding their relative impulsiveness and inability to withstand negative life events, compared with young adults who are raised with siblings.

Official documents released by the Ministry of Health indicate the magnitude of the problems in the death registry system. In 2006, a document on the official Ministry of Health website (2006 N.O.154) (3) reported that many deaths go unreported (e.g., the province with the highest rate failed to report 86.3% of deaths). Furthermore, many deaths are not reported to the registry system in a timely manner (e.g., one province had substantial delay in reporting 70% of all deaths). The lack of a comprehensive and reliable death registering system in present-day China has led to inadequate detection of many suicide deaths (4). In addition, China has no reliable epidemiological data regarding suicide on university campuses.

The lack of mental health services is an urgent problem for campus populations in China. Beijing has approximately 700,000 university students. Yet, as of 2006, there were only 108 mental health counselors at various universities in Beijing (5). The shortage of mental health professionals results in a greater risk for undetected and inadequately treated mental health crises. The Chinese university system would benefit greatly by attention to this serious problem.

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