A casual reader of the article by Kaur et al. in this issue of JMCP might find the results unimpressive for the intervention with buprenorphine-naloxone in 1 large managed care plan. Persistence with this intervention therapy to treat patients with a history of prescription opioid use was only 48% at month 1, 27% at month 6, and 20% at month 12. Even for the small proportion of patients persistent on buprenorphine-naloxone, we do not know any clinical outcome measures including the effect on illicit drug use or prescription opiate use not captured in the pharmacy claims system. And, Kaur et al. found no cost savings in total prescription opiate claims when the cost of buprenorphine-naloxone was included in the analysis.

Misuse of opioid analgesics is a challenge for every health plan, including a greater number of emergency room visits attributable to opioid analgesic abuse than heroin abuse. It is only in the last 8 years that the treatment options for opioid addiction have expanded significantly. For more than 80 years following the 1914 Harrison Narcotic Drug Act, physicians in the United States could not legally prescribe opioid medications for the treatment of opioid dependence. The Harrison Narcotic Drug Act made it illegal for a physician to keep a patient “comfortable by maintaining his customary use.” The only exception to this 80-year prohibition was dispensing of methadone in regulated programs.

On October 17, 2000, the Drug Addiction Treatment Act (DATA) permitted the use of Schedule III, IV, or V narcotics to be used for either detoxification ( tapering) or long-term maintenance. Buprenorphine had been approved by the U.S. Food and Drug Administration (FDA) 15 years earlier, on December 30, 1985. However, the combination therapy with the naloxone was not approved by the FDA for the treatment of opioid dependence until October 8, 2002. DATA permitted each physician with a minimum of 8 hours of approved training in treatment and management of opioid addiction or specialty certification to treat no more than 30 patients with buprenorphine-naloxone. In June 2005, federal regulations were relaxed to permit each physician to treat as many as 100 patients. Both buprenorphine alone (Subutex) or in combination with naloxone (Suboxone) are Schedule III controlled substances that require no special waiver for dispensing by pharmacies, but the Substance Abuse and Mental Health Services Administration (SAMHSA) requires physician registration, and SAMHSA maintains a list of physicians by state who are authorized to treat opioid addiction with buprenorphine.

Buprenorphine is a partial opioid agonist that is administered primarily as an oral sublingual tablet once daily in the dose range of 12 mg to 16 mg. It is appropriate for use only during induction in a clinic setting in which access to opioids can be prevented. In an unsupervised environment in which there is no control over access to illicit opioids, buprenorphine in combination with the opioid antagonist naloxone is preferred. Naloxone is a pure narcotic antagonist that has no agonist effects, and in the presence of opioid agonists causes intense opioid withdrawal symptoms if buprenorphine-naloxone is misused parenterally.

In 2003, Fudala et al. reported the results of an 8-center trial involving 326 opioid-dependent patients randomized to 16 mg buprenorphine per day in combination with 4 mg of naloxone or 16 mg per day of buprenorphine alone or placebo; this clinical trial was used in the application for FDA approval of buprenorphine-naloxone. The proportion of urine samples negative for opiates after 4 weeks of treatment was only 17.8% in the buprenorphine-naloxone group, 20.7% in the buprenorphine only group, and 5.8% in the placebo group (P<0.001). Clark observed in an accompanying editorial that this study—even its open-label phase—was dissimilar from the real world in which physicians can prescribe up to a 30-day supply of buprenorphine-naloxone. Also, the application of the Fudala et al. findings to addiction with prescription opioids is not clear because all of the patients in that study were heroin addicts, with median 7-year duration of use and 2 patients with 35 or more years of heroin use.

More recently in 2006, Fiellin et al. found 40%-44% of urine samples to be negative for opioids in a 24-week clinical trial of 166 opioid-addicted patients treated with buprenorphine-naloxone in a common dose of 16 mg buprenorphine per day, with some patients dosed up to 24 mg per day if there was ongoing illicit drug use or if the patient reported discomfort. The 166 opioid-addicted patients were randomized to 1 of 3 treatment groups: (1) standard medical management and medication dispensing once per week, (2) standard medical management and medication dispensing 3 times per week, and (3) enhanced medical management and medication dispensing 3 times per week. Therefore, the study by Fiellin et al. was primarily a study of the effects of counseling on adherence with buprenorphine-naloxone therapy.

Importantly, neither Fudala et al. nor Fiellin et al. studied conditions similar to treatment of opioid-dependent patients enrolled in managed health care plans. Specifically, in addition to the controlled, supervised environment of these 2 studies and the significant behavioral support in the study by Fiellin et al., these studies excluded many patients who would be treated in managed care.
the real world. For example, Fiellin et al. excluded patients who were dependent on alcohol, benzodiazepine, or sedatives, were psychotic, or had major depression. Also, it is not clear if any of the patients in the study by Fiellin et al. were addicted to prescription opioids, but we do know from later author correspondence that cocaine-dependent patients were excluded from the study.13

In 2007, Mintzer reported the first outcomes from use of combination of buprenorphine-naloxone outside of the controlled environment of a clinical trial.14 Mintzer et al. studied a cohort of 99 patients treated by 3 internal medicine physicians at 2 urban primary care practices: a hospital-based primary care clinic and a freestanding neighborhood health center. All 99 patients were strongly encouraged but not required, to attend meetings of Alcoholics Anonymous (AA) or Narcotics Anonymous (NA). This research found that 54% of patients were “sober” at 6 months, as defined by the treating physician.

The research method used by Mintzer et al. introduces the opportunity for bias because sobriety was determined by the 3 treating physicians who questioned each patient at each visit about possible substance use and attendance at AA or NA meetings and counseling sessions and reviewed adherence to buprenorphine-naloxone. Intermittent urine drug tests were not performed uniformly at both treatment sites. Mintzer et al. also reported that “motivated patients” who did not appear to be adherent were “sometimes offered intensified counseling and/or adjustment of buprenorphine dosage.”

In addition to shortcomings of the undoubtedly well-intentioned but potentially invalid methods employed by Mintzer et al., their outcomes appear optimistic in a more real-world setting. Behavioral support in particular would quite likely be less attentive, less accessible, and less common when buprenorphine-naloxone can be dispensed in up to a 30-day supply. If anything, the study by Mintzer et al. underscores the importance of combining buprenorphine-naloxone with counseling including continued reinforcement of the importance of using group-support resources such as AA and NA.

As with most of the opportunities in managed care, the return on investment (ROI) from an intervention depends on how well the investment is targeted to the patients who are most likely to experience a benefit. Kaur et al. provide us with the second report in the medical literature regarding the use of buprenorphine-naloxone in the real world, although there was 1 observational study of buprenorphine alone reported by Italian researchers that was indexed by MEDLINE in early 2008.15 Unfortunately, Kaur et al. provide us no information to help managed care plans focus an investment in buprenorphine. We know only that the patient population in the observational analysis reported by Kaur et al. was 62% male (n = 32), and approximately 70% (n = 58) were between the ages of 26 and 55, with about 15% each aged 18-25 years (n = 13) and 56-65 years (n = 13). Kaur et al. limited their analysis to patients with at least 1 pharmacy claim for a prescription opioid in the 6 months prior to the index period with buprenorphine-naloxone. Unlike the clinical trials such as Fudala et al. that enrolled only heroin addicts, we do not know what proportion of the patients in the managed care analysis described by Kaur et al. were primarily users of illicit opioids.

Perhaps the real-world research by Mintzer et al. might be helpful in describing the patient characteristics and intervention factors that would predict a higher ROI from intervention with buprenorphine-naloxone. Yielding the only information that we have at this time for the use of buprenorphine-naloxone in a non-research setting, Mintzer et al. found that 55% of “sober” patients attended AA or NA meetings versus 37% for non-sober patients, but the difference was not statistically significant (P = 0.09), and 36% of the sober patients had private insurance versus 18% in the non-sober group (P = 0.05). While there was no difference in the average dose of buprenorphine-naloxone for the sober group (15.3 mg per day) versus the non-sober group (15.3 mg per day) the mean length of treatment 169 days versus 62 days, respectively, was associated with sobriety (P < 0.01). The work of Mintzer et al. provides hope, albeit through a low quality of evidence, that buprenorphine-naloxone can be used in non-specialized settings to achieve “sobriety” in patients with opioid dependence.

Despite shining some light on the use of buprenorphine-naloxone in a real-world setting, there are several limitations in the administrative claims research described by Kaur et al. The authors acknowledge these limitations, including the unusual research method in which the observation periods were fixed calendar periods rather than a consistent length of follow-up for each patient after the first new buprenorphine-naloxone pharmacy claim (a pre-index period of October 2004 through March 2005; a patient identification period from April 2005 through September 2005; and a post-index follow-up period from October 2005 through March 2006). This study design makes it impossible to describe persistence with the intervention therapy in a reliable or even valid manner. Kaur et al. acknowledge that their fixed-period method of analysis results in some understatement of the mean and median duration of therapy with buprenorphine-naloxone. The effect of this unusual method of analysis on assessment of the prescription opioid use in the follow-up period is less clear. Nevertheless, the unusual method of analysis employed by Kaur et al. may be defensible from a health plan perspective since the intermediate outcome—persistence with the intervention buprenorphine-naloxone therapy—is in some ways secondary to the objective of the intervention: reducing the use and costs of prescription opioids at some point in time in the future for these managed care members. However, to be effective, buprenorphine-naloxone like methadone must be taken indefinitely to substitute for opioid use. It is possible but unlikely that short-term therapy with buprenorphine-naloxone would have any effects at 12 months of follow-up on the use and cost of prescription opioids.
Regarding the investment in the ROI calculation, buprenorphine-naloxone is expensive. The internet price for 90 sublingual tablets of buprenorphine 8 mg in combination with 2 mg naloxone, the only commercially available dose form, is $484.52. Therefore, at the most common dose of 16 mg buprenorphine-4 mg naloxone per day, the cost is $10.76; $323 per month or $3,900 per year. Methadone on the other hand costs just $0.57 per 10 mg tablet, and while buprenorphine-naloxone is superior to placebo in retention of patients in therapy, it is inferior to methadone. More real-world studies are necessary to demonstrate that buprenorphine-naloxone is preferable to methadone, a relatively low-cost option to heroin and to high-cost legal opiates such as controlled-release oxycodone (OxyContyn) and transmucosal fentanyl (Actiq, Fentora).

For health plans, buprenorphine-naloxone can be used to treat members who abuse prescription opioids. From the broader societal perspective, buprenorphine-naloxone may reduce needle-sharing and thereby reduce the spread of human immunodeficiency virus and hepatitis B and C viruses. For health plans and society in general, buprenorphine-naloxone many help reduce the number of emergency department visits for overdose, the number of fatal overdoses, and overall mortality.

So, what are we left with after consideration of the work of Kaur et al.? We do not know if opioid-dependent patients in managed care will benefit from this intervention with buprenorphine-naloxone. Fudala et al. and Fiellin et al. excluded from their buprenorphine-naloxone trials the patients most likely to be candidates for buprenorphine-naloxone intervention in typical managed care settings. Therefore, we do not know if opioid-dependent patients in managed care will benefit from this intervention with buprenorphine-naloxone. More importantly perhaps, we do not know which patients in particular might benefit. It seems a reasonable wager that group support including attendance at AA or NA meetings, combined with dedicated behavioral support from the medical group or health plan, will contribute to the likelihood of successful sobriety. Further, motivation to discontinue opioid dependence is still the undressed factor that is most likely to predict success in reducing dependence on illicit opioid use and licit use of high-cost prescription opioids. At this time, there are no reports in the literature of the effectiveness of buprenorphine-naloxone in reducing opioid use to the point of discontinuation of buprenorphine-naloxone.

REFERENCES