Anticipated and unanticipated consequences of abuse deterrent formulations of opioid analgesics

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The paper by Hwang, et al. in this volume demonstrates that a reformulation of OxyContin (Purdue Pharma, Yonkers, NY, USA) in 2010, which had been intended to discourage opioid abuse, may have had the unintended consequence of discouraging its therapeutic use as well.1 This is an important finding, despite some flaws in the study, which raises important public health concerns. In this context, some history for those not well-versed in the current epidemic of prescription opioid abuse might be helpful.

The abuse problem has its roots in two major developments in the 1990s. The first was a recommendation from the Joint Commission on Accreditation of Healthcare Organizations, which emphasized that pain should be treated as the fifth vital sign, and accordingly, there should be less trepidation about using potent opioids to relieve pain.2 This recommendation led to a surge in the use of opioid analgesics, which resulted in the inevitable diversion of some to those seeking their non-therapeutic effects.3 The second major factor was the introduction of a sustained release formulation of oxycodone—OxyContin—which contained large amounts of pure oxycodone. Sustained release preparations are meant to deliver a drug steadily for 12–24 h, and as a result, it was felt by the company and the Food and Drug Administration (FDA) that OxyContin had very little abuse potential.4,5 This judgment was based on the well-established Pavlovian concept that a delay in reinforcement (i.e., in this case, “getting high”) tends to be minimally effective in eliciting an operant response (i.e., drug taking). What the FDA and the manufacturer did not anticipate was the cleverness of illicit drug users. It was quickly established that the sustained release mechanism could easily be breached by crushing or solubilizing the oxycodone, making available large quantities of the active ingredient for snorting or IV injection. OxyContin quickly became the most widely abused and diverted prescription opioid, commanding very high prices on the black market.5,6

As the abuse crisis worsened over a 20-year span, intense government and other regulatory efforts grew to slow the supply of these drugs. Chief among the major steps was the adoption of prescription monitoring programs, which facilitated dual efforts to clamp down on script doctors and, most importantly, patients who “doctor shopped”.7 Other, equally strong measures were joint efforts by federal and state regulatory bodies to eliminate pill mills and the rise of police organizations across the country with dedicated programs to stop the diversion of prescribed substances.8 One additional measure, strongly supported by the FDA, was the development and introduction of abuse deterrent formulations (ADFs) of opioid analgesics.8 Because all drugs meant for oral consumption must be bioavailable and soluble in the gut, very little can be done to reduce abuse by the oral route. Rather, the exclusive purpose of these formulations is to make it difficult to extract the drug by chewing or crushing for inhalation or intravenous use, arguably the most harmful forms of substance abuse.9 Thus far, several products have been developed with abuse deterrent properties, a reformulated OxyContin ADF and Opana ER (oxymorphone, Endo Pharmaceuticals

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Inc., Dublin, Ireland)—both of which contain mechanical barriers to prevent tampering—and at least one, Suboxone, which contains buprenorphine and the opioid antagonist naloxone. The theory with the latter being that naloxone at the dose utilized would block the high produced by buprenorphine, discouraging its use intravenously or by inhalation. However, there are now reports that users, particularly internet-savvy ones, have found a simple method to separate buprenorphine and naloxone, based on their physico-chemical properties, making supplies of buprenorphine readily accessible.10

As mentioned earlier, by far the most commonly used and studied ADF is the reformulation of the very popular OxyContin that was introduced in 2010. Most studies11–15 to date have found that the ADF has been effective in reducing the abuse of OxyContin—up to a 35–40 percent reduction. However, an unanticipated consequence was that the change in formulation drove many former users to select a different opioid to use instead, including some who shifted to IV use and inhalation of heroin.11–13 The paper by Hwang, et al. is one of the first to explore another, potentially more worrisome consequence of the introduction of ADFs: do they influence the therapeutic use of these important drugs? These authors found that overall use of OxyContin decreased upon the introduction of the ADF, after statistically accounting for the impact of generics, which came and went during the time interval studied. Assuming these corrective factors were properly applied, one could conclude that OxyContin’s therapeutic utility—at least to the extent that prescriptions reflect purely therapeutic use—decreased after the introduction of the ADF with no apparent compensatory increase in the use of other opioids, a puzzling finding which begs for further directed studies (e.g., how was pain treated in those for whom OxyContin was effective but no longer prescribed?).

With respect to the observed decrease in the prescriptions of OxyContin, several explanations seem possible. First, this could reflect less doctor shopping on the part of problematic patients because of the decreased appeal of OxyContin; second, similarly, disreputable physicians (i.e., script doctors) may be writing fewer prescriptions for OxyContin because of a drop in demand; third, physicians may be less likely to use OxyContin because the introduction of the ADF, and the new label insert stressing its abuse deterrence, produced a more heightened awareness of its abuse potential; fourth, insurance programs may not be willing to reimburse the higher cost of the ADF, relative to other, less expensive non-ADFs of other opioids; finally, there may be a real or perceived change in the ease of use or efficacy of the new formulation relative to the old. The study by Hwang, et al. used pharmacy sales and, therefore, can shed no light on any of these possibilities. Clearly, direct studies with physicians and patients are needed and it is our hope that this paper will stimulate such research. Although we have little data to back up our speculations, we suspect that all of these factors may be at play.

The finding that sales of ADF OxyContin are reduced relative to the initial formulation seems counter-intuitive to some extent. Before the advent of abuse deterrent formulations, it was widely felt that an ADF would, if anything, increase its use to some extent, the reasoning being that without concerns about abuse, physicians would be more inclined to use an ADF. There appears to be little data to support this logical conclusion, which begs to be explained in more directed studies.

Despite discussions about abuse deterrent formulations, it is clear to these authors that we are focusing too much on the supply side of the prescription opioid epidemic. While efforts to make it more difficult to obtain these drugs and divert them from therapeutic channels are certainly important, we need to be careful that these preparations do not lead abusers to abandon licit opioids in favor of heroin. Clearly, what is needed are sustained efforts to address the demand for these drugs because history tells us that as long as there is a demand for a drug, that demand will be met in some way.

The paper by Hwang, et al. is one step forward in the direction of examining the impact of ADFs on the appropriate use of these medications in the treatment of pain. While this strength of the paper is obvious, it can’t be ignored that there are some limitations, most of which are acknowledged by the authors. A huge database provides a great deal of statistical information but lacks the ability to discern why physicians or patients make the decisions they do. Moreover, this database does not permit a within subject design, which would help understand what impact the ADF had on particular physicians or patients. Despite these important limitations, this study should serve as a springboard to stimulate more hypothesis-driven research in an extremely important area of research.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES