

A practical and ethical solution to the opioid scheduling conundrum

Michael E Schatman¹
Beth D Darnall²

¹Foundation for Ethics in Pain Care, Bellevue, WA, USA; ²Stanford University School of Medicine, Division of Pain Medicine, Palo Alto, CA, USA

Abuse-deterrent formulations (ADFs) of opioids have been in existence since the 1970s,¹ with abuse-deterrent mechanisms including physical barriers (eg, barriers to crushing), chemical additives such as opioid antagonists or irritants, and prodrugs that require conversion of the medication into their active forms in the gastrointestinal tract.² A recent systematic review and meta-analysis³ found no difference between ADFs and non-ADFs in terms of efficacy or adverse events including nausea, vomiting, dizziness, headache, somnolence, constipation, and pruritus. Notably, the efficacy of ADFs in preventing abuse is not yet established, and therefore the authors could only comment on their “potential ... to deter or resist some of the common forms of tampering associated with opioid misuse and abuse”. While Turk et al² have elucidated the complexity of producing high-quality research on the efficacy of ADFs to reduce opioid abuse, recent data are encouraging. For example, since Purdue Pharma’s (Stamford, CT, USA) voluntary reformulation of OxyContin[®] to an ADF in 2010, abuse of the medication has decreased significantly.⁴⁻⁶ As a specific example, National Poison Data System statistics indicated a 36% reduction in abuse exposure for OxyContin following ADF reformulation. Meanwhile, researchers for Purdue Pharma found an increase in abuse exposure for other single-entity oxycodone products and a 42% increase in abuse exposure for heroin during the same time frame.⁷ Although OxyContin has been the most investigated abuse deterrent formulation, ADFs of other opioids have demonstrated promise in preliminary investigations.^{8,9}

Data have indicated that despite being home to only 4.6% of the world’s population, the US consumes 80% of the world’s prescription opioid analgesics.¹⁰ The overreliance of Americans on prescription opioid analgesics for chronic noncancer pain has brought into question the integrity of the nation’s pain care system, not just in the US,¹¹ but in the eyes of the international pain community.¹² After more than a decade of problems related to opioid use and misuse (eg, overprescription, fraudulent marketing,¹³ diversion, abuse, overdose deaths¹⁴), and denial of the iatrogenic complications of opioids,¹⁵ various factions of government have initiated measures to control opioids, measures that have been referred to as the “war on opioids”. As is the case in any “war”, casualties abound. For instance, the collateral damage associated with reducing access to opioids in the US has been an increase in the abuse of other drugs, often black tar heroin, in people who previously had access to prescription opioids.¹⁶ Although experts have called for the establishment of a “middle ground”,¹⁷ such a balance has been elusive, especially in the US.

Correspondence: Michael E Schatman
Foundation for Ethics in Pain Care,
1601 114th Ave. SE, Suite 100,
Bellevue, WA 98004, USA
Email headdock@comcast.net

In the US, drugs are scheduled-based according to the Controlled Substance Act of 1970, which designates drugs into one of five schedules based upon medicinal value, harmfulness, and potential for abuse and addiction.¹⁸ Schedule I drugs are those considered to have a high potential for abuse with no medicinal value, Schedule II drugs have a high potential for abuse with medicinal value, Schedule III designates drugs that have a lower potential for abuse than Schedule I and II drugs, Schedule IV drugs have a low potential for abuse, and Schedule V drugs are thought to have an abuse potential even lower than those designated as Schedule IV.¹⁸ The vast majority of opioids prescribed orally for analgesia are classified as Schedule II drugs, with the exceptions being certain codeine compounds and hydrocodone compounds.¹⁹ Due to a controversial 1971 decision by the US Food and Drug Administration (FDA), hydrocodone was given a “split” Schedule, with pure hydrocodone (which was unavailable in the US until October 2013) designated as a Schedule II and hydrocodone in combination with a nonopioid analgesic (hydrocodone combination drugs) assigned Schedule III status.²⁰ The problem with this designation is that there is no evidence that hydrocodone combination drugs are any less abusable than is pure hydrocodone. Accordingly, the FDA convened early in 2013 to consider upscheduling hydrocodone combination drugs from Schedule III to Schedule II. Critics of the potential upscheduling of hydrocodone combination drugs claim that, should this occur, patients and physicians will suffer great inconvenience (as Schedule II drugs require a hard copy prescription and cannot be automatically refilled), resulting in a deleterious impact on pain management.²¹

The scheduling of opioid analgesics in the US does not take into account whether the medication is an ADF or a non-ADF. In fact, all ADFs currently available on the US market are classified as Schedule II drugs. We find this schema of scheduling to lack consistency with the purpose of the scheduling classification system. Presumably, the goal of classifying a drug as Schedule II versus Schedule III is to provide appropriate safety structures, thus creating an abuse deterrent system. Accordingly, one would expect that ADFs would be classified as Schedule II and non-ADFs as Schedule III. Despite efforts to improve risk mitigation within medical practices through opioid agreements, pill counts, urine drug testing, and prescription monitoring programs, the lethality of prescription opioid analgesics in the US has continued to increase, based upon the most recent available Centers for Disease Control data.²² Prescription opioid abuse is not likely to simply “go away”, and the 16,000+ prescription opioid-related deaths that occur annually in the US²² are not likely to decrease unless manufacturers

and the FDA cooperate in an effort to make all prescription opioids available only as ADFs. Concern regarding the costs of ADFs has been voiced^{23,24} and indeed, the American health insurance industry has at times refused to provide coverage for these potentially life-preserving medications.²⁵ ADFs have been posited to have specific value in treating patients at high risk for prescription opioid abuse.^{26,27} However, Stanos et al²⁸ have opined that: “Limiting prescription of tamper-resistant opioid formulations to patients assessed to have an elevated risk of abuse may prove ineffective if these patients can obtain traditional prescription opioid formulations from another source.”

As opioid prescription increases in other developed and less developed nations as well,²⁹ problems with abuse, diversion, and overdoses are increasing in tandem.³⁰ The World Health Organization “ladder” for pain relief³¹ also does not take into account abuse-deterrence, and therefore an update to this international classification system should be considered. Indeed, the continued relative ease of access to non-ADFs is a serious international concern that merits examination (and appropriate revision) of existing systems of classification in all nations. This may be accomplished by encouraging a relatively simple and practical scheduling system that appropriately classifies opioids based on each drug’s formulation and its associated risk profile. Such a system would create a logical, inverse relationship between opioid access and risk, and thus would optimize patient safety.

Disclosure

The authors report no conflicts of interest in this work.

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