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Research design considerations for clinical studies of abuse-deterrent opioid analgesics: IMMPACT recommendations

Dennis C. Turk[1], **Alec B. O'Connor**[2], **Robert H. Dworkin**[2], **Amina Chaudhry**[3], **Nathaniel P. Katz**[4], **Edgar H. Adams**[5], **John S. Brownstein**[6], **Sandra D. Comer**[7], **Richard Dart**[8], **Nabarun Dasgupta**[9], **Richard A. Denisco**[10], **Michael Klein**[11], **Deborah B. Leiderman**[12], **Robert Lubran**[3], **Bob A. Rappaport**[11], **James P. Zacny**[13], **Harry Ahdieh**[14], **Laurie B. Burke**[11], **Penney Cowan**[15], **Petra Jacobs**[10], **Richard Malamut**[16], **John Markman**[2], **Edward Michna**[17], **Pamela Palmer**[18], **Sarah Peirce-Sandner**[2], **Jennifer S. Potter**[19], **Srinivasa N. Raja**[3], **Christine Rauschkolb**[20], **Carl L. Roland**[21], **Lynn R. Webster**[22], **Roger D. Weiss**[6], and **Kerry Wolf**[23]

[1]University of Washington

[2]University of Rochester

[3]Johns Hopkins University

[4]Analgesic Solutions and Tufts University

[5]Covance

[6]Harvard Medical School

[7]Columbia University

[8]Denver Health Authority and Rocky Mountain Poison & Drug Center

[9]University of North Carolina

[10]National Institute on Drug Abuse

[11]United States Food and Drug Administration

[12]CNS Drug Consulting

[13]University of Chicago

[14]Endo Pharmaceuticals

[15]American Chronic Pain Association

[16]AstraZeneca Pharmaceuticals

[17]Brigham and Women's Hospital

[18]AcelRx Pharmaceuticals

[19]University of Texas Health Science Center San Antonio

[20]Johnson & Johnson Pharmaceutical Research & Development

[21]Pfizer

[22]Clinical Research & Pain Clinic

[23]NAMA Recovery

Address all correspondence to: Dr. Dennis C. Turk, Department of Anesthesiology & Pain Medicine, Box 356540, University of Washington, Seattle, WA 98195; turkdc@uw.edu; fax: (206) 543-2958..

Abstract

Opioids are essential to the management of pain in many patients, but they also are associated with potential risks for abuse, overdose, and diversion. A number of efforts have been devoted to the development of abuse-deterrent formulations of opioids to reduce these risks. This article summarizes a consensus meeting that was organized to propose recommendations for the types of clinical studies that can be used to assess the abuse deterrence of different opioid formulations. Due to the many types of individuals who may be exposed to opioids, an opioid formulation will need to be studied in several populations using various study designs in order to determine its abuse-deterrent capabilities. It is recommended that the research conducted to evaluate abuse deterrence should include studies assessing: (1) abuse liability; (2) the likelihood that opioid abusers will find methods to circumvent the deterrent properties of the formulation; (3) measures of misuse and abuse in randomized clinical trials involving pain patients with both low risk and high risk of abuse; and (4) post-marketing epidemiological studies.

Keywords

Abuse; Abuse Deterrent Formulation; Abuse Liability; Opioids; Risk of Abuse; Study Design

1. Introduction

The number of prescriptions for opioid analgesics has increased substantially over the past decade [39,51]. In the United States, opioid analgesics were the most commonly prescribed medications in 2009, accounting for 202 million prescriptions [71]. Coinciding with the increasing use of opioids, prescription opioid abuse has become a significant public health problem [20,23,28]. In 2010, there were 2 million new initiates to nonmedical use of prescription opioids in the United States, a number that surpassed all other substances of abuse with the exception of marijuana [63]. Along with the increase in prescription opioid abuse, there have been substantial increases in the number of substance abuse treatment admissions for addiction to prescription opioids [64] and in the number of prescription opioid-related emergency department visits and overdose deaths [39].

Chronic pain and opioid addiction are clearly interrelated, though many facets of the relationship have been incompletely defined. The percentages of chronic pain patients who develop opioid abuse after being prescribed opioids are uncertain, but estimates have ranged from less than 1% to more than 18% [34,35] and may be substantially higher in vulnerable populations [65]. Some investigators have found evidence of aberrant drug-related behavior in more than 40% of patients when assessed by urine toxicology screen with [48] or without [72] behavioral monitoring. At the same time, the prevalence of chronic pain is high among individuals with opioid addiction [73]; for example, in a study of 248 methadone maintenance patients, 61% reported chronic pain [42]. A personal history of drug or alcohol abuse and a family history of substance abuse appear to be predictors of aberrant drug-related behavior, but there remains a paucity of good evidence to guide providers in the prediction of which patients with pain will develop aberrant drug taking behavior in response to receiving prescription opioids and also in the management of pain in patients at increased risk of aberrant drug taking behavior [19,68].

The development of abuse-deterrent formulations (ADF) of opioid analgesics should theoretically allow treatment of pain while reducing the rate of prescription opioid abuse and related adverse outcomes [44]. An ADF might present a public health advantage if it reduced the likelihood of: (1) pain patients progressing to opioid abuse or addiction; (2) recreational users escalating their abuse and developing addiction; (3) established

individuals with addiction developing complications related to their condition; or (4) reducing accidental ingestion or overdose-related morbidity and mortality. Unfortunately, an opioid formulation may reduce the likelihood of one of these outcomes while simultaneously producing unintended adverse effects within another population. For example, many clinicians and investigators initially thought that sustained-release oxycodone would be relatively abuse-deterrent because its slower onset and longer duration of action would produce less euphoria (which is thought to promote addiction) than immediate-release oxycodone. However, sustained-release oxycodone became a widely abused prescription drug after entering the market, at least in part because the sustained-release mechanism can be circumvented by crushing the tablet (resulting in a rapid release of drug and subsequent powerful euphoric effect) [20]. The potential for such unintended consequences suggests that rigorous testing using a variety of research designs and subject populations is necessary to evaluate the abuse deterrence of an opioid analgesic formulation adequately.

2. Methods

In June 2009, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), a consortium representing academia, governmental agencies (e.g., Food and Drug Administration [FDA], National Institute on Drug Abuse, and Substance Abuse and Mental Health Services Administration), pharmaceutical companies, and patient advocacy and research organizations, convened a two-day consensus meeting with the aim of developing consensus recommendations for the types of clinical studies that would be needed to assess the abuse deterrence of opioid analgesic formulations. Participants were selected for their expertise in research, administration, or clinical care related to opioid abuse, or in clinical research and treatment involving chronic pain. The consensus meeting was designed to reflect broad representation of relevant disciplines and perspectives while limiting the size in order to promote fruitful and efficient discussion.

A set of background articles was circulated prior to the meeting [1,5,19,21,28,44,55]. In addition, lectures were presented covering the scope of opioid abuse (R. Denisco), pre-clinical and clinical research design issues (E. Adams, S. Comer, N. Dasgupta, N. Katz, M. Klein, D. Leiderman, J. Zacny), and epidemiologic approaches (J. Brownstein, R. Dart).

3. General issues

Several different types of ADFs of opioid analgesics have been or are currently being developed with the potential to reduce abuse without affecting analgesia (see examples in Table 1). Typically, these methods have been designed to deter the risk of tampering by those seeking to abuse the medication, rather than reducing the risk of developing abuse or addiction among patients who had been taking the medication as prescribed; however, it is possible that reducing tampering might decrease progression to abuse or addiction.

The best evidence that an opioid formulation is truly abuse deterrent would be the demonstration that, after adjusting for potential confounders, the total rate of prescription opioid abuse declined substantially after prescriptions for the ADF largely replaced other prescription opioids available [10,44,55]. Such data could only be collected after a formulation has become available and only if the formulation essentially replaces other forms of prescription opioids available. Evidence that a specific ADF is not abused after its use becomes established would also be compelling. Because epidemiologic data only become available after approval and marketing of the formulation, other methods would need to be used to determine whether a formulation is *likely* to have a lower risk of abuse than alternative prescription opioids before it becomes available.

As described below, there are numerous considerations related to the design of a study that seeks to assess the abuse liability of an opioid formulation. Fundamentally, the central aims of the study must be clearly identified, and these will affect the choice of the best study population and study design. Each of the study designs described below has strengths and limitations, and these must be carefully weighed when selecting among them to address specific questions and when results of the studies are interpreted. Since each study will, by necessity, be designed to answer only very specific questions in selected populations, the overall abuse liability of an opioid formulation will be best established by evaluating the results of a number of complementary studies employing varied methods and different populations.

3.1. Definitions

One challenge in interpreting the literature is the lack of uniform definitions of abuse-related terms among investigators, regulators, and clinicians [18]. In order to maintain consistency throughout the meeting, the definitions of abuse and misuse that were developed by a previous panel of experts were used. Specifically, *misuse* was considered "use of a medication (for a medical purpose) other than as directed or indicated, whether willful or unintentional, and whether harm results or not," and *abuse* was considered "any use of an illegal drug or the intentional self-administration of a medication for a nonmedical purpose such as altering one's state of consciousness, for example, getting high" [45].

A distinction should be made regarding the level of evidence available that a medication formulation is truly abuse-deterrent. We will use the term "putative abuse-deterrent formulation" (*p*ADF) to refer to a formulation that has a theoretical basis for potentially being abuse-deterrent. The term "likely abuse-deterrent formulation" (*l*ADF) will be used to refer to a formulation for which there is a body of evidence from clinical trials and other research but not epidemiologic studies suggesting that the formulation may be abuse-deterrent. Methods of evaluating the likelihood that a formulation is genuinely abuse-deterrent are described below. Finally, we reserve the use of ADF for formulations that have been shown to be *l*ADFs and to actually reduce abuse relative to other opioid analgesics in high-quality epidemiologic studies, possibly supplemented by results of large-scale clinical trials in chronic pain patients with abuse endpoints.

The level of evidence required by the medical and scientific communities for a formulation to be considered an *l*ADF rather than a *p*ADF is difficult to specify. In general, it is recommended that the results of a mosaic of studies be evaluated before a *p*ADF can be considered likely to be abuse-deterrent (i.e., *l*ADF), and that individual formulations will need to be considered on a case-by-case basis incorporating careful consideration of the features of the formulation, and the number, types, and quality of the studies supporting abuse deterrence. This research should include studies assessing: (1) the "likability" of the formulation; (2) the likelihood that opioid abusers will find methods to circumvent the abuse-deterrent properties and make the formulation highly abusable (e.g., identifying methods to convert the opioid into an injectable or inhalable form); (3) misuse or abuse outcomes in randomized clinical trials (RCTs) involving pain patients with both low and higher risk of abuse; and, if possible, (4) epidemiological data. These distinctions are intended to be considered and balanced with other available information regarding the formulation.

3.2. Choice of comparator

A *p*ADF purports to be abuse-deterrent *relative to existing formulations*. Studies intending to demonstrate abuse deterrence will generally need to compare the *p*ADF to comparable dosages of the most similar existing formulation of the opioid (e.g., if a *p*ADF is developed

for an extended-release formulation of an opioid, the *p*ADF would typically be compared with the *non*ADF extended-release formulation of the opioid). If no existing formulation exists, such as with a new molecular entity, comparisons with a well-characterized opioid-agonist at what are likely to be equianalgesic dosages can be conducted [76]. Biased dosing, such as lower dosing of the *p*ADF relative to the standard formulation, must be avoided, as abuse liability relates not just to the formulation but also to the dosage. Longer-acting opioids will generally require higher dosages administered less frequently in clinical scenarios to produce plasma concentrations that are comparable to short-acting opioid formulations administered more frequently (i.e., the total mg administered in 24 hours should be comparable). In some circumstances, additional comparison with other opioids or *p*ADFs may be useful for demonstrating the *relative* abuse deterrence of different treatment options, but these should supplement rather than replace comparison with the standard opioid formulation.

3.3. Populations to consider in study design

A significant challenge in studying the potential abuse-deterrence of opioid formulations is the broad range of patients and non-patients who can ingest prescription opioids. It is possible that a formulation could reduce the likelihood of abuse among patients who take the drug as prescribed and yet be highly sought by abusers because it can be easily manipulated into a form that can be administered nasally or by injection. The ideal ADF would provide effective pain relief with no additional side effects relative to the *non*ADF medication but would reduce the risk of abuse among patients using it properly and overdose among both patients and non-patients who take it.

Another important consideration with many of the potentially abusing populations is the possibility of an interaction between alcohol and the opioid formulation. A problem with some long-acting opioid formulations is accelerated absorption (“dose dumping”) when co-ingested with alcohol, which can produce severe respiratory depression and potentially death. Given the prevalence of alcohol use by recreational opioid users [54], individuals with opioid dependence [77], and even pain patients prescribed opioids [4], it is important to examine interactions with alcohol. The decision regarding whether to exclude subjects with active or past histories of alcohol abuse from studies of ADFs requires careful consideration because these individuals will be exposed to opioid formulations that reach the market.

Because of the wide range of individuals who can be affected by opioid ingestion, no single study can assess all of the at-risk populations, with the possible exception of large-scale epidemiologic studies. Therefore, it will be necessary for a formulation to undergo testing in different populations at risk using different research designs.

3.3.1. Young children—The rate of prescription opioid poisoning among young children has recently been examined [5]. The vast majority of incidents involved opioids prescribed to a family member, and the rate of incidents correlated with the volume of opioid analgesics prescribed within the community. Although young children do not typically abuse opioids, formulations that reduce the appeal to children and which, if ingested, are less likely to result in harmful outcomes, would be advantageous.

3.3.2. Recreational abusers—The age range and other demographic characteristics of recreational abusers (i.e., those who take prescription opioids for their euphoric effects) are broad. An opioid formulation that produces less euphoria in this population would probably be less likely to be abused, have less street value, and be diverted less frequently. Ideally, progression from recreational abuse to addiction would be reduced or even eliminated.

3.3.3. Patients with acute pain—In the absence of significant substance abuse risk factors, the likelihood of a patient with acute pain who is prescribed opioid analgesics becoming an opioid abuser is thought to be quite low [23], but there is very little evidence supporting this belief. Some pain patients do report experiencing euphoria when taking opioid analgesics for acute pain [6], which raises the possibility that these patients could develop opioid abuse. Because opioids are commonly prescribed for diverse types of acute pain, they contribute to the available supply of opioid analgesics used by recreational abusers and those with addiction. However, most *p*ADFs in development are long-acting formulations that would be relatively unlikely to be prescribed for acute pain; therefore, the impact of *p*ADFs on the development of abuse in individuals prescribed opioids for acute pain, whose risk is already thought to be low, is likely to be minimal.

3.3.4. Patients with chronic pain—Although the percentage of patients with chronic pain who develop a substance use disorder as a result of medical use of opioids is thought to be relatively low, evidence of aberrant drug-related behavior, perhaps due to pre-existing substance abuse, is more common [41,72]; the absolute numbers affected may be substantial. Given the estimated 116 million people with chronic pain in the United States alone [22], with many millions more worldwide, even a small decrease in the rate of abuse could result in substantial public health benefits.

3.3.5. Established opioid addiction—A formulation that resists tampering and manipulation by those with opioid addiction may have relatively lower demand and thus would be less likely to be diverted. In addition, the number of clinically significant overdose events related to such an ADF would likely be low. Although established addiction will not be eliminated by the existence of ADFs, the total number of individuals abusing prescription opioids may decline over time or progression to more dangerous routes of administration may be reduced if an ADF replaces a substantial proportion of prescribed *non*ADF opioids within a community.

4. Study design considerations

Several different research designs can help establish the potential abuse deterrence of an opioid formulation. The main categories of these studies are summarized in Table 2 and are discussed below.

4.1. Human abuse liability (HAL) assessment

This term is used to describe small, highly controlled studies of the pharmacodynamic properties of potentially abusable drugs, typically assessed with measures of subjective drug effects in experienced drug abusers. Whether an opioid formulation is abused appears to depend on the interplay of at least three factors: (1) the inherent positive characteristics of the drug (e.g., “likability”), which is related to the time to onset of effects, side effects, and other properties; (2) formulation factors, including the ease with which the formulation can be converted into alternate (“preferred”) routes of administration, such as snorting, smoking, or injecting; and (3) societal factors, such as the availability of the drug relative to alternatives, peer influences, cost, and stigma [11].

HAL assessment studies can be used to assess and compare the relative likability of different formulations of a drug. The results of these studies can be used to estimate the likelihood of abuse of intact and tampered formulations, and such data may also be relevant to the development of abuse and addiction in patients taking the drug as prescribed. These studies are useful [37], but favorable data from such studies are not sufficient to demonstrate the abuse deterrence of a formulation. There are examples of drugs that seem to have less abuse liability as measured by subjective responses, such as ratings of drug “liking,” and yet self-

administration of the drug seems discordant with these findings [21]. For example, the combination of buprenorphine and naloxone has a theoretical basis for abuse deterrence (injection of the combination should provide naloxone antagonism of the effects of buprenorphine). This combination has been shown to be less "liked" by intravenous abusers and to have one-half the street value of buprenorphine alone in Finland [2], but a case series from Malaysia suggests it might be associated with increased amounts of injection doses, benzodiazepine injection, and needle sharing [9].

HAL studies can be performed in several ways. A common approach is to use a randomized, double-blind, placebo-controlled cross-over design studying a relatively small number of subjects with histories of recreational drug abuse or addiction. Typically, several outcomes are assessed within four main domains: (1) subjective effects (e.g., likability, street value), (2) physiological responses (e.g., pupillary constriction, respiratory rate), (3) drug self-administration behavior (e.g., discrete choice experiments, including drug A vs. drug B or drug A vs. a monetary choice, for example, $20), and (4) cognitive and psychomotor performance (e.g., measures quantifying the degree of impairment resulting from drug intoxication) [45]. Outcome measures are usually repeated to determine the time course of the effects, such as the time to onset, to peak, and to offset.

Typically, these HAL studies use a positive control, such as a standard formulation opioid, to assess relative abuse liability, and should show a dose response for the positive control [17,37]. For a *p*ADF, various doses should be studied, including supra-therapeutic doses if possible. Ideally testing should include the intact formulation and also the formulation after it has been tampered and modified in ways likely to be used by prescription opioid abusers [45].

HAL assessment studies are commonly performed in individuals who are not interested in obtaining treatment of their abuse but who can be considered "experienced users" with regard to the intoxicating effects of the class of drugs being examined. Although the specific characteristics of the subjects enrolled in these studies have varied, individuals with chronic pain have generally not been included, in part because of difficulties interpreting the data (e.g., do patients like the opioids because they reduce pain or because they feel high?). However, conducting these studies in pain patients would potentially provide useful information about the likely effects of a *p*ADF, particularly if results are compared to results obtained in non-pain populations. Testing in several different populations could lead to greater understanding of the level of abuse liability that could be expected in the community.

Several methodologic decisions must be made prior to designing a HAL study. These include the population that will be studied, the method to be used for administering the *p*ADF, the outcome measures, and the definition that will be used for detecting a clinically important reduction in abuse liability. Unfortunately the predictive validity of these studies has not been systematically examined; this is an area in urgent need of additional research. Recommendations regarding outcome measures for these studies, based on the best available evidence, will be presented in a forthcoming IMMPACT manuscript.

4.2. Opioid extractability testing and "kitchen chemistry" studies

Several different types of prescription opioid abusers have been described, in part reflecting variability in preferences for different opioids and different routes of administration [10,45]. There appears to be an association between the duration of abuse and the likelihood of progressing from oral ingestion to more "advanced" routes of administration, such as injection [10]. The creativity and sophistication of abusers' abilities to convert *p*ADFs into abusable formulations is well-established [24]. One predictable phenomenon is that abusers of opioids and those with addiction will attempt to manipulate any new opioid formulation

in a manner that produces greater euphoria (e.g., nasal inhalation or injection). Formulations that are resistant to a specific type of tampering can be identified but strategies to circumvent the deterrent properties are likely to be widely disseminated once such strategies become known.

In order for a new opioid formulation to be considered an *l*ADF, it would need to be evaluated in studies designed to determine how readily it can be converted into a form that is more abusable. Two categories of studies should be performed. These include studies in controlled laboratory settings, assessing the ease and completeness of extraction of the opioid using standard measures (e.g., crushing or grinding the pill or capsule or dissolving it in water or alcohol). Exactly which procedures should be performed on a formulation and how the ease of extractability should be quantified has been explored elsewhere [46], but consensus recommendations are needed.

Formulations that appear to be resistant to tampering in controlled laboratory settings can be characterized further by subjecting them to "kitchen chemistry" studies. In these studies, opioid abusers have been provided with the formulation and basic kitchen and chemistry supplies and implements (e.g., razor, hammer, coffee grinder) within a controlled and observed setting. Whether subjects can extract or convert the opioid into a more desirable form is then assessed, and the ease (e.g., number of steps involved, complexity of the steps, time required) and success (e.g., proportion of the opioid that is extracted, desirability of the extracted opioid) of extraction are determined. For obvious reasons, the results of these studies are typically not publicly disclosed, but they can be used in determining whether a product should be further developed.

Since opioid abusers have different preferred routes of administration and different experience in extracting opioid preparations, studying a variety of different types of abusers and those with addiction, such as those who snort, smoke, or inject, is important. Several additional methodological issues must be addressed when designing these studies, such as the sample size and types of subjects, what basic "supplies" should be available, and how the results of these studies should be interpreted.

4.3. Analgesic RCTs and their potential role in assessing abuse deterrence

Two critical requirements of any *p*ADF are that the formulation must provide analgesic efficacy and that it must not produce significant adverse effects beyond those normally expected in pain patients taking the medication as prescribed. It is possible that a formulation intended to reduce abuse, such as a pro-drug or agonist-antagonist combination, would possess less analgesic efficacy than the standard formulation of the same opioid. Similarly, certain formulations, such as those containing an opioid mixed with a noxious chemical intended to reduce injection, might produce significant adverse effects within a population of pain patients. For these reasons, *p*ADFs should be assessed carefully in RCTs designed to measure analgesic efficacy and adverse events. These trials will be most useful if they contain at least three arms—placebo, active comparator with equianalgesic dosages of a standard opioid formulation, and the *p*ADF. The assessment of efficacy and tolerability of *p*ADFs should adhere to previous recommendations regarding chronic pain clinical trials [31,32,66,67] to the greatest extent possible**.**

Traditionally, analgesic RCTs have enrolled a relatively specific and well-defined patient population, which helps ensure the internal validity of the trial. Patients at high risk for opioid abuse are generally excluded. However, some of the excluded populations may be those most likely to derive benefit from a *p*ADF. For this reason, studying both narrow and broader, more inclusive patient populations in analgesic clinical trials is important.

4.3.1. Assessing potential abuse—A number of symptoms, behaviors, and outcomes that suggest the possibility of opioid misuse or abuse within an analgesic RCT may be assessed retrospectively. These include the presence of certain critical events, such as euphoria, sedation, and overdose; incidents that are potentially related to opioid abuse, such as loss or theft of study drug from individuals or study sites; and any evidence of misuse or abuse, for example, as reported by family members. The rates of each of these potential indicators of abuse should be compared between different groups, and a systematic analysis of the reasons for premature terminations from the trial should be performed.

Because retrospectively obtained data are likely to be less comprehensive, sensitive, and reliable than prospectively designed and assessed outcomes, RCTs examining the analgesic efficacy of a *p*ADF should also prospectively assess signs of opioid misuse and abuse within the trial subjects. In addition to defining and capturing the information described above, trial personnel should be trained to recognize potentially aberrant behaviors. Additional measures to detect opioid misuse should be collected, including, for instance, urine drug tests and monitoring for evidence that subjects obtained opioids from other providers, forged prescriptions, or diverted study medication [41]. Consideration should also be given to administering standardized opioid risk screening tools, such as the revised Screener and Opioid Assessment for Patients with Pain [14,19] and instruments designed to detect opioid misuse, such as the Current Opioid Misuse Measure [13,19,50]. However, the reliability and validity of such assessments need to be confirmed in large, prospective studies [19,50,68].

4.4. RCTs with misuse or abuse-related outcomes as primary endpoints

One important example of an RCT specifically designed to detect opioid misuse can serve as a model for how trials can be designed to compare rates of abuse between different opioid formulations [1]. In this trial, over 11,000 chronic pain patients were assigned to one of three arms: tramadol (the compound being assessed for abuse risk), randomized treatment with either tramadol or a non-steroidal anti-inflammatory drug (NSAID) (a control that is not typically abused), or randomized treatment with either tramadol or a hydrocodone-containing compound (a control that is sometimes abused). Patients were followed for one year, during which nine interviews occurred. Opioid misuse was measured using a novel "Abuse Index" that consisted of scores of 0 or 1 in each of four domains: (1) inappropriate use (patient must have increased dose on own without physician approval and never skipped or forgotten a dose); (2) use for purposes other than analgesia (must have two or more of following: takes more when upset or discouraged, for intoxicated feeling, or for putting patient in a "good mood"); (3) patient unable to stop use (at least one of following: physician told patient to stop or cut down, subject tried to stop and found doing so at least somewhat difficult, or patient believes stopping use would be difficult); and (4) evidence of opioid withdrawal using a 24-question survey.

In this trial [1], presumptive abuse or dependence was defined as at least two out of the three criteria if a withdrawal score was not obtained, or three out of four criteria if a withdrawal score was obtained (a withdrawal score was captured only if patients discontinued their medication). Following the initial prescription, physicians could prescribe any of the three options to patients, and analysis was performed according to whichever treatment was taken at the time of the interview. The rates of presumptive abuse or dependence were similar for tramadol (2.7%) and NSAIDs (2.5%), but significantly higher for hydrocodone (4.9%). Strengths of this study include its size, use of both positive and negative controls, and use of a power analysis to estimate the necessary sample size (though the details of this analysis are not presented in the manuscript). The rates of abuse or dependence were low in this study; however, it is possible that urine drug testing or other methods could have detected additional cases of misuse. Interviewers were trained using structured interviews in the

detection of signs of abuse and addiction. Critical to the success of obtaining honest information from patients was the fact that interviewers made it clear that responses would be kept anonymous to the study physicians. These results should be interpreted with some caution because physicians were able to change the analgesic prescribed after the initial assessment, possibly due to pain severity or patient preference, and analgesic outcomes were not reported.

Features of an RCT of a *p*ADF to evaluate misuse and abuse outcomes in pain patients that should be considered in the design of the trial include: (1) randomization to *p*ADF, a comparable standard opioid formulation, placebo, and, if possible, a treatment with known low abuse potential; (2) use of a representative, diverse population of chronic pain patients, including patients with histories of abuse; (3) blinding of investigators assessing outcomes, such as whether a patient is misusing their medication; (4) use of validated measures to detect misuse, abuse, and addiction; (5) detailed training study personnel to whom patients will be exposed; (6) evaluation of suspected cases; and (7) comparison of the pain relief and adverse effects associated with each treatment arm to ensure that reduced abuse liability is not achieved at the cost of reduced pain relief or increased adverse events.

4.5. Post-marketing epidemiologic studies

Safety, including potential adverse events related to opioid abuse, can be carefully measured in RCTs, but the information provided is inadequate to evaluate the safety and impact of a drug in real-world use. Exposure to a drug is tightly controlled in a clinical trial, limiting the ability to predict what will happen when the drug is introduced into broad usage. As described, high-risk patients are often excluded from clinical trials, so how they will respond after the drug is introduced into the market is unknown. The amount of drug to which patients can be exposed is limited in clinical trials, whereas the dosage and duration of use may be considerably greater in the community. Importantly, the sample sizes of clinical trials are small in comparison to the population that may be exposed after the drug is introduced to the market, so infrequent adverse events can often be detected only after the drug becomes commercially available. Performing surveillance and epidemiologic studies during conditions of actual drug use after a drug is approved and becomes widely available provides invaluable information about its safety and whether a formulation is truly abuse deterrent. Epidemiologic databases offer the fundamental advantage of recording events during use, misuse, and abuse of a drug in real life under multiple conditions and by various types of individuals within large populations. Thus, epidemiologic studies can confirm or refute, in a naturalistic setting, laboratory assessments of abuse liability.

Post-marketing surveillance, the monitoring of medications and pharmaceutical products or devices after their release on the market, is required in the United States as well as other countries. The goal of post-marketing surveillance is to detect adverse events that might not have been apparent during the review and approval process. In the United States, the Food and Drug Administration maintains a database to support post-marketing surveillance for all approved products. The Adverse Event Reporting System (AERS) includes information obtained through voluntary reporting from health care practitioners and consumers. Pharmaceutical product manufacturers receive reports of adverse events from the public and from health care practitioners, which they are required to report to the FDA, and many have developed reporting systems for this purpose. These databases capture spontaneous reports by patients, physicians, family members, and manufacturers, among others. Reliance on spontaneous reports introduces limitations that can only be addressed in comprehensive pharmacovigilance systems, such as those maintained in a number of European companies.

Post-marketing surveillance is an important tool to identify diversion, abuse, and other adverse events. In addition to monitoring by the FDA and drug manufacturers, surveillance

systems have been designed to identify abuse and diversion in multiple populations [12,25]. Several different epidemiological databases and surveillance programs are available for evaluating misuse of prescription controlled substances in the United States and are discussed below and in the Appendix.

4.5.1. Limitations of epidemiologic studies—A fundamental challenge in the study of prescription opioid misuse is acquiring data of sufficient quality and precision to be able to draw meaningful conclusions. For example, post-marketing surveillance systems for opioid analgesics must provide sufficient product specificity to allow comparison of different formulations of the same opioid (e.g., an immediate-release vs. an extended-release formulation vs. a *p*ADF of the same opioid). It is also important to determine how individuals are administering a product, such as whether they are taking it orally in intact form, orally after grinding it, or inhaling, smoking, or injecting it. Ideally, surveillance systems can also capture basic demographic and clinical information, such as whether the population using the opioids consists of patients for whom prescription opioid analgesics are intended. Unfortunately, many data sources are not designed to specifically address the population of chronic pain patients.

Analysis of real-world data will contain the potential for substantial bias and confounding due to the uncontrolled design, and bias may be particularly hard to assess in epidemiologic studies. Comparison of various groups must be interpreted thoughtfully because unrecognized differences may influence the results. These differences may be present at baseline or occur in the form of confounders during treatment (e.g., co-morbid diseases or concomitant medications). It is also difficult to compare databases because of differences in data collection methodology (e.g., intended purpose, duration, frequency) and definitions of misuse, abuse, and other variables. For example, misuse of an opioid may be assessed by collecting acute adverse health events reported to poison control centers, by studying the diversion of the drug in law enforcement encounters, and by surveying patients under treatment for opioid dependence or addiction. Examining multiple epidemiological databases and assessing their agreement (a strategy of “multiple perspectives” or “multiple detectors”) can partly overcome these challenges, allowing one to better understand the misuse of a drug.

Studying longitudinal cohorts of drug abusers is an additional method that can provide detailed information and can address the difficulty in measuring potential confounders [15,70,75]. It is unlikely that a longitudinal cohort will be nationally representative, but local cohorts allow changes to be monitored over time as the drug market adapts to a new opioid formulation and can provide in-depth information about shifts in drug use and consequences (both intended and unintended).

4.5.2. Surveillance systems and epidemiologic databases used to monitor prescription drug misuse and abuse in the United States—Many databases have been used for epidemiologic studies of prescription drug misuse and abuse in the United States, and each has strengths and limitations. Proper interpretation of their data requires an understanding of these limitations, which are summarized in the Appendix. Typically, these databases acquire information when individuals misusing or abusing drugs are forced to reveal themselves. For example, databases such as the Drug Abuse Warning Network (DAWN), the National Poison Database, or the poison center component of the Researched Abuse, Diversion, and Addiction-related Surveillance (RADARS) System acquire data on persons experiencing health events that prompt someone to contact a poison center or take them to an emergency department. These systems collect unique information, but are based on spontaneous reporting; that is, data on the individual is not collected unless someone contacts a poison control center or goes to an emergency department. Other databases, such

as the Addiction Severity Index-Multimedia Version, the Opioid Treatment Programs, and Survey of Key Informant Patients, collect data when a patient enters treatment for substance abuse. To the extent that these databases capture a representative subset of those entering substance abuse treatment they can be considered cross-sectional in nature.

Specific limitations of existing databases also depend on the study hypothesis and objective of the investigation. For example, if information on a specific product is needed (e.g., hydrocodone with acetaminophen), systems such as the National Addictions Vigilance Intervention and Prevention Program and the RADARS System can be useful because they identify the specific product. Federally funded longitudinal surveillance systems of drug abuse epidemiology (e.g., Monitoring the Future and the National Survey on Drug Use and Health) provide population-based estimates of overall abuse and contain little drug-specific information. The timeliness of data availability is another important consideration. Many databases release results two or three years after collection, which prevents prompt detection of changing trends. The geographic specificity of the data also varies between databases. At times, specific localization of drug misuse activity may be more helpful than national data; for example, national estimates would not identify the regional hotspots of Appalachia and the east coast of Florida that have been especially active areas of prescription opioid abuse and increasing mortality related to prescription drugs, especially opioid analgesics, over the past few years in the United States. We have highlighted surveillance systems and epidemiologic databases in the United States for illustrative purposes. Similar systems are available in other countries with each having their own strengths and limitations.

4.5.3. Other sources of epidemiologic information on pADFs—Several other sources of information can be useful for assessing the presence and nature of potential confounders in the cross-sectional data sources described above. We have grouped these additional data sources into three categories: (1) medical utilization studies examining administrative claims data; (2) focused studies, including those in localized geographic areas; and (3) anecdotal sources, such as the internet or news media. Although the supportive studies described below do not provide strong evidence of abuse-deterrence taken individually, they can provide complementary information that can inform the interpretation of studies using the databases described above.

4.5.3.1. Medical utilization studies: Medical utilization studies examining commercial “sales” data and administrative claims data are necessary to understand how prescription medications are used in routine medical practice. Samples of commercially available sales data can be analyzed to estimate how many prescriptions for a drug have been filled and how many patients have been exposed to the drug in a country or region. These data can be used in evaluating abuse-deterrence to understand the market penetration of a new formulation. If there were low sales volume and very little abuse reported, it would be valid to question if the low abuse rates were due to the inherent nature of the formulation or were a result of limited utilization. Data from prescription monitoring programs could also be harnessed for this purpose [47].

Claims data collected during routine medical care by health insurance companies, health maintenance and managed-care organizations, and publicly-funded health benefit programs can also be examined. These data are often available for research purposes and can include patient medical records and pharmacy claims for office and hospital visits, procedures performed, diagnostic tests, clinical diagnoses, and drugs dispensed. Used widely in comparative effectiveness research and pharmacoepidemiologic assessments of adverse events, claims data may provide insight into the medical use of *p*ADFs. In the simplest analysis, the opioid formulations that patients received could be considered the exposure, and diagnoses and other outcomes occurring after initiation of treatment related to drug

abuse could be compared—for example, treatment for substance use disorder or overdose, or suspicious medication accounting concerns (e.g., repeated early refills). Although relatively straightforward to conduct, the lack of adjustment for treatment allocation in such a study makes interpretation of the results particularly problematic.

One of the central limitations with claims data comparing two drugs (e.g., a traditional opioid and a *p*ADF) is that we do not know the reason why a clinician prescribed one drug instead of another (or no drug at all), a type of confounding that RCTs avoid through randomized allocation to treatment conditions. Even without abuse-deterrence labeling, clinicians may conclude that a drug has abuse-deterrent properties, influenced by the specifics of the formulation, colleagues' experiences, and non-regulated information sources. Patient selection in this manner would be a form of "confounding by indication" if the outcome to be measured is one related to prescription drug abuse. Put another way, the same factors that would lead a physician to prescribe a *p*ADF (e.g., substance use history, psychiatric co-morbidities) are those that would make the individual more likely to experience the outcome (e.g., patterns of medication use that suggest abuse problems, overdose).

For this reason, claims data should be used extremely carefully when comparing unadjusted rates of abuse-related outcomes between opioid formulations. At a minimum, assessments of exchangeability and adjustment for treatment allocation and confounding by indication are required, using such approaches as instrumental or latent variables [36], propensity score matching [43], disease risk scores [3], marginal structural models [33], and other techniques [40,49], with results supported by sensitivity analyses [38]. Another difficulty with some of these sources of data is that many of the potential confounders (e.g., drug abuse history) are not likely to be recorded in clinical charts, possibly requiring external data collection to assess the nature and degree of confounding prior to adjustment [62]. Additionally, those who are abusing their medications may pay out-of-pocket to fill some or all of their prescriptions and therefore avoid having the extent of their use captured in the claims data. The other major limitation of claims data is that abuse-related outcomes are relatively rarely identified in the claims data and have not been externally validated, with limited understanding of the extent and nature of misclassification (but see [74]).

Claims-based studies do have the potential to provide contextual information on the medical use of a *p*ADF prior to conducting causal modeling. For example, when a *p*ADF is first marketed, only specialists may prescribe it or the drug may be prescribed to an inherently different patient population (in terms of demographic or underlying disease characteristics) than those receiving the traditional formulation. Health insurance plans may place a *p*ADF on restricted formularies due to cost, and those who receive the *p*ADF may be individuals who have had to demonstrate eligibility criteria; alternatively, some third-party payers may not cover or may place barriers (such as prior authorization) that limit access of individuals with certain types of coverage to a *p*ADF. In either of these cases, the population that receives the pADF will differ in important ways from the eligible treatment population, and interpretation of the data will require an understanding of these potential confounders. These are hypothetical scenarios that can be informed by analyzing claims data because the purpose of these studies is not necessarily to make a causal inference, but rather to understand the nature of the medical use.

4.5.3.2. Focused studies: Focused studies or rapid assessments can be conducted in a limited geographic area (e.g., city or county, a large hospital or nursing home), leveraging researchers' existing connections with a community. Focused studies may enroll fewer participants than the national data systems, but they allow for more in-depth questioning about reasons for using or not using a *p*ADF and can provide information about an

individual's history and allow for follow-up of a cohort as market shifts occur. These studies may be easier, less expensive, and faster to conduct compared with large national cross-sectional studies. Although the generalizability of the results of focused studies can be questioned, a great deal has been learned from cohorts of injecting drug users and persons with opioid addiction [7,16,53,56,57,60].

In order to provide credibility to observations made using large national databases, it is essential to simultaneously monitor conditions in the broader illicit market of prescription opioids and illicitly manufactured opioids for potentially confounding influences. For example, a sustained increase in the availability of cheap refined heroin may lead to a decrease in the desirability of all prescription opioids among nonmedical users. In the opposite circumstance, sudden decreases in heroin or "black-market" prescription opioid availability may create conditions where individuals are willing to use whatever opioid is available, even if they are ADFs or formulations that would be less desirable when more choices are available. In these cases, the relative rates of abuse may be due to the social environment in which the drugs are consumed rather than the inherent nature of the formulation. Supply limitations are often geographically localized, but if they occur in enough places, they may influence national data. Indeed, efforts are underway to cause exactly this kind of shift in the illicit market for prescription controlled substances, such as through expanded use of prescription monitoring programs in the United States. Assessing these external forces is critical to understanding whether population-level changes in patterns of abuse may be attributable to new opioid formulations rather than to changes in the availability of other opioids.

Surveys of active drug users are also important for understanding potential safety concerns arising from methods to circumvent abuse-deterrent mechanisms. The "abuse-deterrent" formulation of temazepam in the United Kingdom in the 1990s and Australia in the 2000s offers a graphic example of unintended consequences associated with circumventing ADFs that led to greater morbidity among injecting drug users. Although the formulation was intended to reduce injection misuse, it apparently did not do so, but it did appear to be responsible for an increased rate of injection site complications [8,27,29,30,58,59,61]. For formulations intended to deter crushing and injecting, participants recruited from syringe exchange programs and drug treatment programs may offer considerable insight into the perception of new opioid formulations in the addiction community [27].

4.5.3.3. Anecdotal reports: Anecdotal reports are likely to play a role in the initial perception of the effectiveness of a *p*ADF once it enters the market. Lags in data collection and publication time for major national data sources create a vacuum for information that will naturally be filled by anecdotal reports.

Anecdotal information is not formally considered in most plans for the evaluation of *p*ADFs, but nevertheless shapes public opinion and should be monitored because of the wealth of data it may provide and for hypothesis generation. For example, internet postings about prescription medications from drug abusers have been considered in FDA Advisory Committee meetings [69], suggesting that anecdote might play a role in medical decision making. Initial reactions after a drug is launched among drug users and pain patients can provide clues regarding how consumers perceive the drug, and internet postings in drug user forums and news media reports can be early warning signs for safety signals associated with new medications [26], such as the consequences of tampering with a *p*ADF. Similarly, blogs and internet forums for pain patients may suggest that an opioid formulation has previously undocumented benefits or harms that can be studied formally. Taken together, the power of anecdotal reports lies in the ease of reporting and their ability to be quickly disseminated; as electronic communication and social media continue to expand, text-based anecdotal reports

from consumers are likely to play an increasing role in evaluation, with reasonable expectation that these sources be monitored.

5. Conclusions

Opioid analgesics are essential to the management of pain in many patients, but opioids, particularly higher dose formulations, are also associated with significant risk of abuse, overdose, and mortality. Due to the many types of individuals who may be exposed to opioids, an opioid formulation will need to be studied in different populations using a mosaic of different study designs to evaluate its abuse-deterrent properties. To demonstrate abuse deterrence comprehensively, a formulation would ideally need to: (1) show abuse deterrence in a set of studies in non-pain patients, patients with acute pain, and patients with chronic pain, as described above, and (2) show a lower than expected rate of abuse and overdose in epidemiologic surveillance studies making use of complementary databases such as those discussed. Of course, epidemiologic data can only be generated after a formulation has been introduced into the general population, so some of these data cannot be generated prior to drug approval by regulatory agencies.

Table 3 provides a summary of the recommendations we have discussed throughout this article. It is unlikely that a *p*ADF will show measurable benefits in all populations studied and using all of the different research designs we have discussed. Relative judgments of the clinical and social importance of the benefits will likely be necessary; for example, a *p*ADF that reduces the ease of an opioid being ground up and injected will not eliminate all abuse of the drug, nor will it be likely to benefit any but the most high-risk patients. At the same time, incremental reductions in the risk of overdose, hepatitis, HIV, and death among intravenous drug abusers would be meaningful.

Once an ADF is developed, its cost will be an important consideration. The value of ADFs to patients and to society will depend directly on the cost of the drugs and the degree to which they are used. An expensive ADF may be worse for pain patients because some of the cost will likely be passed on to them and high cost may impair access to pain medication. Intravenous opioid abusers will likely revert to other opioid formulations, including heroin, and therefore not truly benefit from a reduced risk of overdose from an ADF. Whether the societal value derived from modest reductions in the rates of relatively uncommon events justifies increased costs resulting from the use of *p*ADFs in pain patients will be difficult to determine. Nevertheless, the ongoing epidemic of prescription opioid abuse requires the development of strategies to curtail abuse while providing pain medications to those who need it, and ADFs are likely to remain a key strategy in the future.

A number of important limitations of the available literature are described above. Research is needed to evaluate the ability of HAL studies to predict real world abuse. In addition, careful assessment of misuse, abuse, and diversion using validated instruments should be embedded in analgesic clinical trials assessing new opioid formulations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Examples of different types of putative abuse deterrent formulations of opioids

Formulation mechanism	Mechanism of deterrence	Potential advantages	Potential disadvantages
Physical barrier	Resists conversion into alternative forms (e.g., barrier that impedes crushing or dissolving)	May reduce likelihood opioid can be converted into a form that can be snorted or injected	Difficult to prevent conversion into all forms that could be abused; potential that certain barriers might reduce ease of use for patients
Chemical additives			
Opioid antagonist (e.g., naloxone)	Counteract opioid effects if oral route bypassed (oral ingestion of antagonist is poorly absorbed)	May reduce non-oral administration	Potential for reduced analgesic efficacy
Irritant (e.g., capsaicin or niacin)	Produces noxious reaction if oral route bypassed or excessive dosage taken	May reduce likelihood of use of excessive dosage	Potential for noxious effects among non-abusers; possible ceiling dosage for patients
Prodrug [a]	Requires conversion of opioid into active form in gastrointestinal tract	Specifically targets non-oral route of use, might reduce likelihood of overdose with excessive oral dosage (if conversion mechanisms are overwhelmed)	Potential for reduced analgesic efficacy; possible ceiling dosage for patients (if conversion mechanisms are overwhelmed)

[a]Regulatory agencies may consider a prodrug to be a “new molecular entity” subject to its own controlled substances scheduling rather than a new formulation of an existing drug.

Table 2

Categories of clinical studies that can be used to assess the potential for reduction in abuse of putative abuse-deterrent formulations

Category of study	Goal of study	Description	Advantages	Disadvantages
Human abuse liability assessment	To estimate the likelihood that a drug will be abused	Study participants (usually opioid abusers) given drug in controlled settings with likability and other abuse liability-related effects assessed	Can suggest the likelihood that intact or tampered formulation will be abused	Artificial settings; typically non-pain patients studied with intact formulation only; may not predict real world abuse
"Kitchen chemistry"	To predict the likelihood and methods by which a drug will be manipulated by abusers	Experienced opioid addicts are allowed access to the drug and basic tools (e.g., for grinding or shaving or dissolving) to elucidate the ease of manipulation of the drug	May provide useful information about how a drug may be manipulated by opioid addicts	Artificial setting; may not uncover methods of manipulation that would be discovered and disseminated in the community
Analgesic RCT	To determine the analgesic efficacy and tolerability of the drug	Standard RCT methodology, but capture evidence of misuse or abuse within the study population (e.g., using urine drug screens)	Strong experimental design	Existing trials typically use highly selected (and potentially unrepresentative) samples excluding the highest risk patients; probably not very sensitive to detecting abuse or misuse. Could be improved by the inclusion of more representative samples
Abuse RCT	To measure rates of abuse in pain patients	RCT designed and powered to detect abuse as a primary outcome	May be best method of determining relative likelihood of abuse in pain patients	May need very large sample sizes depending on risk level of population and event rate of outcome; need appropriate analgesic comparator; clinical and epidemiologic significance of differences unknown
Epidemiology	To estimate within a population the rates of abuse, addiction, and overdose	Different detection methods to track opioid-related adverse effects within a defined community	Best evidence that a formulation is having intended effects on all relevant populations with "real world" use	Comparability of different groups uncertain (e.g., highest risk patients most likely to be prescribed the abuse deterrent formulation); requires significant population usage to detect signal; requires monitoring over long time intervals; quality of data often uncertain; confounding may render interpretation difficult or create misleading results

Table 3

Recommendations for clinical research to evaluate abuse-deterrent formulations of opioid analgesics

1	Adopt standard definitions of misuse, abuse, and addiction
2	Conduct studies assessing: • Abuse liability, for example, in recreational substance abusers • The likelihood that opioid abusers will find methods to circumvent the deterrent properties of the formulation • Misuse and abuse outcomes within randomized clinical trials enrolling low risk and high risk of abuse pain patients • Post-marketing epidemiologic data
3	Features of a randomized clinical trial of a putative abuse-deterrent formulation (*p*ADF) to evaluate misuse and abuse outcomes in pain patients that should be considered in the design of the trial include: • Randomization to *p*ADF, equianalgesic dosages of a comparable standard opioid formulation, placebo, and, if possible, a treatment with known low abuse potential; if no standard formulation exists, such as with a new molecular entity, consider comparisons with a well-characterized mu-opioid receptor agonist at what are expected to be equianalgesic dosages • Use of a representative, diverse population of pain patients, including high risk patients with histories of abuse • Prospective assessments of signs and symptoms of opioid misuse and abuse • Trial personnel should be carefully trained to recognize potentially aberrant behaviors • Blinding of investigators assessing outcomes • Use of validated questionnaires and other measures to detect misuse, abuse, and addiction (e.g., urine drug screening) • Clinical evaluation of potential cases • Careful evaluation of pain relief in the different treatment groups to ensure that reduced abuse liability is not achieved at the cost of reduced pain relief • Reasons for premature terminations from the trial should also be carefully evaluated.
4	Post-marketing surveillance should be used to examine misuse, abuse, addiction, diversion, and other adverse outcomes