Monitoring risk: Post marketing surveillance and signal detection

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A B S T R A C T

The primary goal of postmarketing surveillance is to provide information for risk assessment of a drug. Drugs affecting the central nervous system form a unique group of products for surveillance because they are often misused, abused, and diverted. These medications include opioid analgesics, stimulants, sedative-hypnotics, muscle relaxants, anticonvulsants and other drug classes. Their adverse events are difficult to monitor because the perpetrator often attempts to conceal the misuse, abuse and diversion of the product. A postmarketing surveillance system for prescription drugs of abuse in the U.S. should include product specific information that is accurate, immediately available, geographically specific and includes all areas of the country. Most producers of branded opioid analgesic products have created systems that measure abuse from multiple vantage points: criminal justice, treatment professionals, susceptible patient populations and acute health events. In the past, the U.S. government has not established similar requirements for the same products produced by generic manufacturers. However, the Food and Drug Administration Amendments Act of 2007 includes generic opioid analgesic products by requiring that all products containing potent opioid drugs perform rigorous surveillance and risk management. While general risk management guidance has been developed by FDA, more specific analyses and guidance are needed to improve surveillance methodology for drugs which are misused, abused, diverted.

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1. Introduction to risk management

Risk management is the process of assessing a product’s benefits and risks, followed by developing and implementing tools to minimize its risk. The goal is to maintain the benefits of a drug while reducing the risks as much as possible. Ultimately, the balance of benefits and risks determines whether the drug will be withdrawn from the commercial market, or in the case of new drug applications, approved or disapproved.

The importance of risk management has been recognized by the U.S. Food and Drug Administration (FDA) for many years (Leiderman, in press). The FDA defines three phases of risk management: (1) risk assessment, (2) surveillance, and (3) intervention (FDA, 2005a,b,c). These phases form a cycle that is repeated to provide continual assessment and intervention and optimize the benefit-risk ratio of a drug.

Often, the importance of surveillance in the process of risk management is overlooked. At the time of initial marketing, the data available to evaluate the risks of a medication are limited. Information regarding chemical structure, abuse liability in animals and humans, and clinical trial data allow useful characterization of many risks (Carter and Griffiths, in press). Pre-marketing risk assessment before drug approval could be improved by development of standards for assessing tamper-resistance, improved animal models that can address formulation-related variables (e.g., onset, duration), and the redesign of human laboratory studies providing appropriate models for comparing formulations (Grudzinskas et al., 2006). Although risks can be identified before marketing and addressed in a risk management strategy, some risks will not become apparent until after the drug is in widespread use in multiple populations. These events are detected by postmarketing surveillance, which provides data for intervention as well as informing potential revisions to the risk management assessment.

Postmarketing surveillance is a core component of risk management because without data to guide interventions, risk assessment is based largely on expert assessment, which is based in turn on premarketing information. While a useful and important adjunct in decision making, expert assessment can be misleading. Numerous medications have been approved for marketing, for example, only to receive warnings or be withdrawn because expert assessment did not identify specific problems during the pre-marketing phase. For examples, see the FDA list of new warnings and withdrawals of marketed drugs (FDA, 2009b).

2. Postmarketing surveillance

Postmarketing surveillance is the practice of monitoring a pharmaceutical product or device after it has been released on
the general market. Pharmaceutical products have been subjected to various forms of postmarketing surveillance for as long as drugs have existed. Today, some type of postmarketing surveillance is required for all pharmaceutical products in the U.S.

Pharmaceutical manufacturers have developed extensive adverse event reporting systems that accept spontaneous reports of adverse events from patients or health care professionals. In some cases, adverse event surveillance can identify a new, but real, risk when an unexpected event is reported and, perhaps, followed by reports of a cluster of similar or related events. For example, when a report to a pharmaceutical manufacturer revealed that a patient developed fulminant hepatic failure during treatment with troglitazone (Rezulin), a hypoglycemic agent for the treatment of diabetes mellitus (Faich and Moseley, 2001), this previously unrecognized risk was documented and triggered a regulatory response. Detailed analysis of individual cases and perhaps the discovery of other cases allows the identification of potential associations between drug exposure and the event. After a relationship has been identified, more focused data collection and analysis allow the manufacturer and the FDA to investigate the events and take appropriate action.

The adverse event has typically indicated undesired effects that occur during intended use of a product. The discovery of congenital malformations after the use of thalidomide during pregnancy occurred during the normal therapeutic use of the drug in pregnant women. Conversely, adverse drug effects that occur with non-therapeutic intent are often not considered adverse events. For example, toxic epidermal necrolysis (TEN) during the use of phenytoin is a well-known adverse event, but respiratory arrest and coma following abuse of an opioid is generally considered separately because it is the expected pharmacological effect of an intentional overdose. In truth, all unintended effects of medication use, even abuse and intentional overdose, are adverse events that should be reported.

3. Pharmacosurveillance of CNS drugs

Increasingly, the FDA has required pharmaceutical companies to provide information on the benefits and risks of newly marketed products. Perhaps the best known example of FDA-required risk management is isotretinoin (Accutane), but manufacturers of many other drugs have been required to perform risk management activities in recent years (FDA, 2005d). The FDA has also proposed the concept of Risk Evaluation and Mitigation Strategies (REMS). Many of the drugs targeted for REMS evaluation as prescription opioids. These requirements are likely to become more stringent because of the increased powers granted to FDA by the Food and Drug Administration Amendments Act of 2007 (FDA, 2007).

The fundamental assumption, and greatest weakness, of pharmacosurveillance is that patients and doctors will report the adverse effects of the drugs they prescribe or use. Unfortunately, patients and health care providers are notoriously poor at reporting adverse events even when alerted to high-risk drugs. Even after the FDA alerted physicians about troglitazone-induced liver failure and requested regular liver testing, compliance was inadequate (Graham et al., 2001).

Poor reporting of adverse events becomes even more likely when the doctor or patient (or both) attempts to conceal the adverse effects of a drug. There may be reluctance to report adverse effects of a drug in at least three circumstances:

- Drugs with effects that are desirable, but not medically needed.
- The best examples are the opioid analgesics. These medications are extremely effective in reducing pain, but also produce desirable psychological effects that foster their use for non-medical reasons.
- Drugs used to treat conditions that the patient may want to conceal. For example, health care providers may accede to patient requests to conceal evidence of HIV infection (i.e. adverse events from HIV medications) or treatment for substance abuse.
- Drugs used to control the behavior of others with malicious intent (i.e. “date rape” drugs, drugs used to facilitate theft, drugs used in child abuse). For example, the victim may not know the adverse effect was produced by the drug and the perpetrator obviously desires to conceal the fact, resulting in non-reporting of adverse events.

3.1. Pharmacosurveillance of drugs that are misused, abused or diverted

Drugs that are misused, abused and diverted share several characteristics:

- Produce desirable psychological and emotional effects.
- Potent effects with rapid onset.
- Produce physical or psychological dependence.
- May be associated with development of addictive behavior.
- May be economically profitable to the user or dealer.

Examples of these drugs include the well-known opioid agonists (e.g. hydrocodone, stimulants (e.g. d-amphetamine), sedative-hypnotics (e.g. phenobarbital) and anxiolytics (e.g. diazepam). However, there are other drugs such as the ketamine or steroids that have desirable effects and are also abused.

The most commonly proposed solution to the dilemma posed by abuse of prescription drugs is to collect information from multiple sources and perspectives. This is a fundamental strategy of most scientific investigation. Scientists cannot directly observe the function of small structures like atoms or molecules and activities like enzymatic action or neuronal transmission. Instead, the consumption of substrate and the products of enzymatic action are measured to infer the mechanism of catalysis. All expected contributors and results of the reaction can be measured to assess the enzyme’s activity from various perspectives and thereby deduce the likely mechanism of action.

In the surveillance of prescription drugs, we can measure the effects of misuse, abuse and diversion in a similar manner. The process of abuse and addiction typically follows a well-described path. This progression is useful in planning surveillance. For example, the phases of drug abuse and addiction include opportunity and initial use, each of which yields measurable outcomes. Initial use may develop into repeated use, which can result in physical dependence as well as addiction in some cases. Addiction (or dependence) is defined as compulsive, out of control use of a drug associated with socioeconomic, behavioral, and legal consequences for the addict (Savage et al., 2003). Prescription drug abuse leading to loss of a job for poor performance is an example of addiction. Since misuse, abuse and diversion occur during each of these phases, data representing each phase should be included in surveillance. The Addiction Severity Index (ASI) measures the substance use, health and social problems of those with alcohol and other drug problems (McLellan et al., 2006) and can be used to assess misuse and abuse of prescription drugs. However, patients in treatment do not adequately represent other groups at risk, for example, college students experimenting for the first time or children who inadvertently ingest a potent opioid. Therefore, surveillance should be designed to address all phases of the addiction pathway.

In addition to measuring all phases of the addiction pathway, a surveillance system should include all populations affected (Table 1). The initial opportunity for drug abuse often occurs at
and Mental Health Services Administration, 2009) uses a national individual into a setting where they can be detected by surveillance as well as patients of other substance abuse treatment programs. Examples of surveillance sites for these populations include methadone programs for treatment of opioid abusing prescription drugs. Examples of surveillance sites for these populations include methadone programs for treatment of opioid abuse as well as patients of other substance abuse treatment programs, and prisons. Patients in substance abuse treatment programs are another important population. These individuals are often knowledgeable about the drugs they use and remarkably creative in diverting and concealing their abuse.

Abuse of a drug often causes an acute health care event. This event offers an important opportunity because it forces the affected individual into a setting where they can be detected by surveillance. The Drug Abuse Warning Network (DAWN, Substance Abuse and Mental Health Services Administration, 2009) uses a national probability sample of hospital emergency departments to collect information on patients with drug related disorders. The National Poison Data System (NPDS, formerly known as TESS) of the American Association of Poison Control Centers collects information from all U.S. poison centers regarding cases they manage. Poison centers can provide fast, product-, and geographic-specific information.

Other important populations include dealers of illicit prescription drugs. Law enforcement programs, drug task forces and state licensing authorities are all examples of programs that are used for surveillance of prescription drug trafficking and abuse.

### 4. Epidemiology of drugs that are misused, abused or diverted

A wide range of epidemiologic efforts have been created to assess drug abuse. Many of these provide useful information about prescription drug misuse and abuse (Table 2). In common usage, surveillance is one aspect of epidemiology. Epidemiological studies generally address more general questions (e.g., What are the national characteristics of prescription drug abuse? What are the national trends in drug abuse? What were the main prescription drugs abused in the United States in the year 2005?). Although there is overlap in the concepts, surveillance is generally referred to more focused measurements of specific events (e.g., in what cities did signal events occur in January 2005?). Surveillance may monitor specific sentinel events or changes in drug use in an area over short periods of time (month, quarter). Epidemiology studies are crucial in providing context and allow surveillance data to be interpreted in the context of the general background of disease.

#### 4.1. The importance of denominators

All surveillance systems produce counts of events. For example, DAWN or NPDS may report that there were 1000 mentions involving exposure to a particular drug. This information is of limited usefulness unless it can be put into a population/setting context (e.g., what population is involved in the area from which the reports originated? How much of that drug was available for misuse, abuse or diversion?). The most commonly used denominator is population. If the surveillance system can identify the location of each event, it can provide population estimates. For example, poison centers report approximately 60 cases of methadone exposure associated with death annually. This information is of limited usefulness by itself, but becomes more useful if we know that these deaths arose from a population of 300 million people, a rate of just 0.2 deaths per one million people in the population (unpublished data, RADARS® System).

A major limitation of population as a denominator, however, is that the amount of drug available for abuse is not considered. If very little abuse of a drug is found, is this because the abuse is actually low or because there was very little drug available in the area for abuse to occur? Conversely, hydrocodone is the most commonly abused opioid drug in most places. Is that because hydrocodone is preferred by abusers or simply because it is the most common drug available?

The person who possesses a drug is similar to the vector of an infectious disease. A patient carrying tuberculosis is only one person, but may spread their infection to multiple individuals. Similarly, a drug abuser may be responsible for distribution of the drug to many other people. In addition, they undoubtedly foster the initiation of drug use by other persons. In order to estimate the availability, it is useful to know how many individuals fill a prescription for a drug. This number is termed as unique recipients of dispensed drug (URDD). URDD is defined as the number of unique individuals that obtain a drug from a pharmacy (Smith et al., 2007). The definition explicitly excludes refills and repeat prescriptions.

The use of the URDD denominator allows for calculation of rates using this indicator of the amount of drug availability in a community. The number of URDD can be obtained for any level of analysis: the drug substance (e.g. oxycodone) or the specific drug product (e.g. OxyContin), a specific geographic area or any combination of geographic areas, and for any period (i.e. one day, one month, one quarter, or one year).

In the case of methadone, an estimate of URDD is 600,000 people in the United States. The rate for methadone-associated deaths when URDD is used as the denominator is roughly 85 deaths per one million URDD. As described above, the rate using population as a denominator yielded 0.2 deaths per million population. Thus, the number of deaths associated with death following exposure to methadone is higher than the population estimate might imply. For comparison, the approximate rate of death for hydrocodone would be much lower, about 5 deaths per one million URDD.
Table 2
Inventory of surveillance sources for controlled substances risk management.

<table>
<thead>
<tr>
<th>Federal surveys</th>
<th>Non-federal systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Survey of Drug Use and Health (NSDUH)</td>
<td>National Poison Data System (NPDS)</td>
</tr>
<tr>
<td>Monitoring the Future (MTF)</td>
<td>National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO)™</td>
</tr>
<tr>
<td>Drug Abuse Warning Network (DAWN)</td>
<td>Researched Abuse, Diversion and Addiction Related Surveillance (RADARS® System)</td>
</tr>
<tr>
<td>DAWN LIVE!</td>
<td>Internet and web monitoring</td>
</tr>
<tr>
<td>National Forensic Laboratory Information System (NFLIS)</td>
<td>Media monitoring</td>
</tr>
<tr>
<td>Treatment Episode Data Set (TEDS)</td>
<td>Sponsor-driven</td>
</tr>
<tr>
<td>Drug Evaluation Network System (DENS)</td>
<td></td>
</tr>
</tbody>
</table>

The URDD concept is meant to address the availability of a drug for misuse, abuse and diversion. Other potential indicators of drug availability include the number of prescriptions written, the weight of drug sold, and the number of defined dosage units sold, among others. Each denominator may be useful in specific circumstances.

5. Surveillance systems for misuse, abuse and diversion of prescription drugs

An effective surveillance system informs risk management decisions by providing current, as well as sensitive and specific information. The timeliness of surveillance data is crucial. However, classic epidemiology studies are carried out over longer periods of time and the results are often reported a year or more after the research was performed. These time frames are very long in terms of drug abuse surveillance. For instance, by the time the results are reported, the abuse conditions in the area may have changed. While traditional epidemiologic studies provide crucial information in terms of general characteristics of abuse, they do not provide information that a risk management program can act upon in a timely manner. Thus, the FDA often requests that surveillance data be provided on a quarterly basis although more frequent monitoring may be needed for specific reasons such as the introduction of a new product. Data for surveillance should be available within weeks or months depending on the precise application of those data.

A surveillance program should also cover all regions within the United States because drug abuse of specific drugs and products can be localized. Again, data generated for a valid national estimate are important, but do not provide all the information needed to allow targeted investigation and intervention. Specific information for every 3-digit ZIP code (or similar specific geopolitical unit) should be available.

Product specificity is also important because not all products are equal in terms of abuse. Generic versions of products may be abused more, less, or the same as their branded counterparts. In some cases, abusers may prefer certain formulations or brand names. Using brand names, for instance, allows an abuser to be more certain that they have not purchased a counterfeit drug. On the other hand, a generic drug may be easier or less expensive to obtain. Further, certain formulations may be easier to abuse. Surveillance systems must be able to identify the specific product accurately and consistently.

Different prescription drugs may also be abused by different portions of the population. For example, individuals initiating abuse of drugs may prefer certain drug products specifically because of their brand name, as noted above (Cicero et al., 2007). Drug dealers may prefer formulations that contain a large amount of the drug so that this can be divided and sold profitably. New initiates often prefer to use a product orally but with time and experience may switch to more potent and riskier injection routes of administration leading them to choose a different formulation.
There are also unintended victims of prescription drug abuse, and surveillance systems may need to include these individuals. For example, pediatric deaths have occurred in association with the use or abuse of prescription opioid products by their caregivers (e.g. pills left within reach of young child) (Bailey et al., 2009). Thus, surveillance systems may need to include pediatric cases. Other potential victims include family members and friends, who may suffer theft, loss of financial support, or potentially infectious complications like hepatitis or human immunodeficiency virus.

The role of quality in data collection and analysis is often neglected. The processes needed to ensure data integrity and accuracy are not used in some systems. Quality control systems are necessary to assure that data are collected appropriately, managed cleanly and reported accurately without sacrificing time. Attentive quality control always reveals sources of errors that can affect the impact of surveillance data. A quality improvement program is needed to address quality issues and assure that the system consistently improves itself.

Groups of surveillance systems have emerged due to the need for multiple perspectives in the surveillance of CNS drugs. For example, the Researched Abuse, Diversion and Addiction-Related Surveillance System (RADARS®, System, www.radars.org) includes multiple simultaneous perspectives on prescription opioid and stimulant abuse. The RADARS® System’s Drug Diversion System provides a criminal justice perspective on prescription drug abuse by surveying more than 300 diversion investigators from jurisdictions in all 50 states. The Key Informant System provides the perspective of substance abuse treatment professionals by surveying approximately 160 designated key informants from a variety of treatment facilities across the United States. The Poison Control System provides information on acute incidents involving prescription drug both in the home and in the emergency care system. Data include acute and chronic exposures for all ages from 47 poison centers, including rural, urban, and suburban areas of the United States. The Opioid Treatment Program System provides the perspective of opioid dependent patients by surveying patients in 75 methadone treatment programs about their individual drug use. The Survey of Key Informant Patients (SKIP) complements the Opioid Treatment Program by anonymously surveying approximately 300 patients nationwide. The College Survey provides information about young new abusers of prescription drugs by surveying 2000 college and university students across the nation. Finally, the Health Care Professional System aggregates information from the other systems that are specific to health care professionals. All of these RADARS System components provide current data every quarter or more frequently.

The Navipro™ system consists of two major proprietary databases and draws from other public databases across the United States (Navipro, 2008). The proprietary databases are ASI-MV Connect and Web informed Services (WIS): internet monitoring and surveys on prescription drug misuse. The public databases used include American Association of Poison Control Centers’ New Core System Database (NCSBeta), FDA-Adverse Event Reporting System (AERS), Drug Abuse Warning Network (DAWN Live!), DEA news, and Medline articles. Other systems are also available (Table 2). Often, manufacturers construct their own systems by melding data from one or more surveillance systems with their own monitoring of adverse events and media surveillance. In some cases, unique approaches have yielded insights into abuser’s perceptions of prescription drugs (Arfken et al., 2003; Woody et al., 2003).

5.1. The role of signals

A signal serves to indicate or warn—like a traffic signal. Implied is an action in response to the signal, like stepping on the brake for a red stoplight. The term signal has been difficult to define because a single case may be a signal (e.g. a death in a naïve adolescent abuser), while in many cases a signal is detected by a cluster of cases or epidemiological analysis.

In the case of prescription drug abuse, a signal identifies a drug, region or other characteristic that exhibits increased misuse, abuse or diversion activity (Dasgupta and Schnoll, in press). For example, a signal may be a rate of abuse for a product that exceeds the predicted rate of cases in a geographic area. For instance, if the rate of reported cases of hydrocodone abuse in an area increases from one calendar quarter to the next, a signal is present and further investigation is needed. Sophisticated statistical methods have been developed to yield signals that are more accurate and specific. However, even a single observation may warrant closer analysis. For example, a death is often considered a sentinel event in drug safety. Similarly, events in young children, health care professionals or other populations may be viewed as signals that should receive further attention or intervention.

A simple analysis often provides illuminating information. For example, plotting of rates by 3-digit ZIP codes for a variety of opioids can reveal geographic hotspots. One challenge is that essentially every 3-digit ZIP code in the U.S. shows some evidence of opioid abuse. Thus, an important goal of surveillance is to detect changes in the rate of a specific products abuse in a specific geographical area. The statistical analysis of surveillance data poses challenges that are beyond the scope of this review, but are described elsewhere (Smith et al., 2007; Dasgupta and Schnoll, in press).

There are three typical responses to the detection of a signal. However it is defined. It can be ignored, studied further, or it can stimulate an intervention. Occasionally, the signal is so impressive that immediate intervention is planned, but the most common response is to perform additional investigation. In many cases, additional surveillance data can help guide further evaluation of a signal. If the surveillance system provides demographic information or geospecific coding, further research can be directed to a specific population or discrete geographic area. Information collected during surveillance can provide a preliminary assessment of who, what, why, where, and, in some cases, how a prescription drug is abused.

After initial exploration of a signal in the surveillance stage, more formal signal evaluation may be needed. This is often provided by a vendor or by the pharmaceutical sponsor itself. Further investigation provides more specific information based on the surveillance information and tries to determine whether an intervention is appropriate. If an intervention appears feasible, this investigation can help focus and guide the intervention. For example, surveillance might indicate that rate of buprenorphine cases has increased in one particular area. The surveillance system may additionally indicate that the signal arises solely from methadone maintenance programs. Using this information, a pharmaceutical company or its representative can contact knowledgeable individuals in the community of concern. If needed, a “SWAT” team can go to the area to perform a rapid in-depth assessment of the area. The resulting information would be used to design interventions to reduce abuse of the drug. For example, a specific formulation of the drug may be abused preferentially. Changes in the formulation may reduce subsequent abuse and reduce the rate of fatal outcomes.

6. Generic CNS medications

Manufacturers of branded products have developed extensive programs to perform surveillance as part of their risk management activities. An important surveillance challenge is that many cases involve generic products rather than their branded counterparts. Using opioids as an example, a physician may prescribe the brand Vicodin® or Percocet®, but the majority of opioid analgesics dispensed by pharmacists are actually generic products, produced by
a generic drug manufacturer. The active substance of branded and generic drugs is identical and their pharmacokinetic parameters similar. While the marketing of generic prescription drugs is indeed different than branded products, abundant information indicates that both generic and branded products are misused, abused and diverted (e.g., Cicero et al., 2007).

Until recently, manufacturers of generic drug products were rarely required to provide all the risk management activities mandated for the original branded product. This approach may change with implementation of The Food and Drug Administration Amendments Act of 2007 (FDAAA). FDAAA expanded the authority of the FDA to require pharmaceutical companies to perform meaningful attempts to reduce the negative consequences of their drugs. Using its new authority, the FDA has proposed that it will require certain drugs to develop explicit Risk Evaluation and Mitigation Strategies (REMS). The purpose of REMS is to reduce the risk associated with a drug, including misuse, abuse and diversion, without impairing access to the drug (Adams, 2009). Extended-release opioids, methadone and the fentanyl patch are among the medications that require a REMS to be implemented (FDA, 2009a). Surprisingly, most immediate-release opioid products have not been required to formulate a REMS. However, immediate-release drugs, nearly all of which are produced by generic drug manufacturers, account for the overwhelming majority of drugs reported to surveillance systems. For example, the number of unique recipients of immediate-release opioid products was 30,814,879 compared to 2,620,255 for modified-release products for October–December, 2008 (SDI, Plymouth Meeting, PA). It seems likely that stringent restrictions on modified-release products does not address all issues with this misuse, abuse and diversion of prescription opioid drugs. Indeed, if efforts are focused on the extended-release products alone, it seems likely that abusers will shift to immediate-release opioid products.

7. Conclusion and recommendations

Assessment of misuse, abuse, and diversion of prescription drugs must address its occult nature and involves fundamentally different surveillance compared to other pharmaceutical products. Current best practice is to use multiple detection systems to assess misuse, abuse and diversion of CNS active drugs by various populations in a timely, sensitive, and specific manner. Data should be available within weeks, to able to detect reasonable changes in abuse rates, and must accurately identify the product(s) involved as well as the specific geographic location. Furthermore, the best surveillance systems also can provide preliminary information about further research and intervention needed in those areas.

Several surveillance challenges persist for manufacturers and regulators of CNS active drugs. The acceptable level of misuse, abuse and diversion has not been defined. The rate of abuse, or the change in the rate of abuse, that warrants intervention has not been defined. Since some level of misuse and abuse occur with all CNS drugs, the FDA and other authorities should begin the process of explicitly designating tolerable levels of misuse and abuse. The tolerable level of diversion must also be defined, but raises different issues because it involves the criminal justice system.

An important emerging issue involves identifying specific drugs that should always require surveillance. The list of drugs reported to be abused is long and many contrasts and contradictions are apparent. While extended-release opioid medications are scrutinized closely, other opioid products seem less closely examined. It seems logical that branded products and products from generic drug manufacturers should be required to have equally rigorous risk management programs. Benzodiazepine drugs seem to receive little attention despite widespread evidence of abuse. Similarly, anticholinergic drugs like diphenhydramine are sometimes abused by adolescents. The effects can be dramatic (hallucinations), but outcomes are generally mild. Perhaps risk management should be required for these drugs as well. Another issue concerns the precise elements that should be required in a surveillance system for abuse of prescription drugs? In the past, a wide variety of systems have been accepted by the FDA. While general risk management guidance has been developed FDA, more specific analyses and guidance are needed to improve surveillance methodology for drugs which are misused, abused, diverted and these activities.

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Conflict of interest

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