Postmarketing surveillance for drug abuse

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Abstract

Assessing actual abuse of prescribed medications requires postmarketing surveillance. In this article we discuss general systems of postmarketing surveillance that exist as of the end of 2002 in the United States and two medication-specific surveillance systems that were devised and tested. The two specific surveillance systems are compared with limitations highlighted. Postmarketing surveillance is in its infancy and requires more research on ways to improve its validity without inducing illicit experimentation. Information on comparator medications is highly recommended both to validate the system and to place the results in context.

1. Introduction

Drug safety evaluation is a mounting concern with news of prescription medication abuse omnipresent. In 2000, 30% of those identified in the US as current illicit drug users reported non-medical prescription medication use (Office of Applied Studies, 2002). Preclinical and clinical behavioral studies may suggest which medication might be abused, but their methods have limited validity (Ator and Griffiths, 2003; Griffiths et al., 2003, this volume). Pre-marketing studies conducted to assess efficacy have limited potential to detect abuse due to the small and select sample participating in clinical trials and the type of protocols typically employed (Brady et al., 2003, this volume). As such, there is a need both to validate the results of behavioral studies and to assess actual abuse of specific medications in the general population at the earliest possible time following their introduction onto the market.

Communication has changed since 1972 when the Controlled Substances Act was passed. News of medications popular in one area of the country (or world) can instantaneously be transmitted to people in other locations via the internet. Moreover, advertisements for medications have changed, reflecting patients’ right to be aware of what new medications are on the market. This change has lead to direct-to-consumer advertising as opposed to relying on direct-to-provider advertising. These two developments, the internet and direct-to-consumer advertising, have diminished historic lags from the time of medication approval to awareness of medications, experimentation, and actual abuse. In response to these changes, regulators and manufacturers are faced with increased pressure to actively monitor for emerging patterns of abuse. In this article we will examine both general and medication-specific surveillance systems for abuse of marketed medications in the United States. The World Health Organization (see http://www.who-umc.org/umc.html for more information; World Health Organization, 2003) and other countries have established registries for spontaneous reports of adverse events after a medication is marketed but will not be discussed in this chapter. Prescription-event monitoring, the systematic follow-up of a cohort of patients exposed therapeutically to the medication, also will not be discussed.

General surveillance systems used in the US have focused on medical consequences of abuse. One system, drug abuse warning network (DAWN), is operated by
the substance abuse and mental health services (SAMHSA) of the Federal government (for more information, see http://www.dawninfo.net, Office of Applied Statistics, n.d.). Operating since 1972, DAWN abstracts medical charts from emergency department admissions and medical examiner’s reports. Starting 1 January 2003 the system is going through an extensive change in geographic coverage and data collection process. Medical records are still abstracted by trained individuals using the physician report of a drug-related admission, but number of drugs and age limitations are changed. For example, information on drugs taken therapeutically will not now be collected (e.g. aspirin for headaches). Also, admissions resulting from accidental ingestion, malicious poisoning or adverse medical reaction will now be abstracted. Summary of the major drug categories and detailed reports are available online with a 6-month-time lag. Real time reporting is also available directly from SAMHSA.

The second component of DAWN is the medical examiner’s reports. These reports beginning in 2003 will cover 48 major metropolitan areas (up from pre-2003 era 21 areas). Unlike emergency department admissions, there will not be national estimates of deaths related to specific drugs. The reports are also being expanded to cover all, as opposed to selected, medical examiners in the metropolitan areas. From these two components, DAWN presents data that can be used to assess emerging medical problems with marketed medications. DAWN is not useful, however, for drugs without serious adverse effects and still relies on providers to document medications and their contribution to the admission/death accurately.

The Food and Drug Administration (FDA) operates another general surveillance system, Medwatch. This system functions as a central depository of adverse event reports (Kessler, 1993; http://www.fda.gov/medwatch; Medwatch, 2002). Practitioners or patients can file a report via paper, phone or the internet. Medwatch was designed as a voluntary system for reporting adverse events requiring medical interventions. It is widely believed to underestimate adverse events associated with medications, especially the longer a particular medication has been marketed and the more well known the adverse effect. Reliance on Medwatch for monitoring abuse patterns is problematic. The person reporting an abuse case using the internet or paper mode must select the adverse event option of “other” and then describe the problem. The textual description then has to be coded. Unfortunately, details from the report may be sketchy, guidelines for coding are lacking, and coders may arrive at different conclusions based upon their training (Woody et al., in press). The lack of promotion of Medwatch for reporting abuse, the underreporting of problems, and the arbitrary coding limit the usefulness of Medwatch for monitoring abuse of marketed medications.

Another source for monitoring medical consequences of medication misuse is the poison control center. The Toxic Exposure Surveillance System is a database covering approximately 96% of all national calls to poison control centers (American Association of Poison Control Centers, n.d. or http://www.aapcc.org). Annual reports list medications by name and contain selected case histories of deaths attributed to medication or other products. These reports serve as sentinel events for unanticipated excessive dosages, administration routes, or combinations with other drugs. As providers become more familiar with treatment for a given drug or product, it is commonly believed that calls for assistance decline.

Other general surveillance systems in the US include treatment admissions to substance abuse programs and community-based surveys. Data on treatment admission to publicly funded substance abuse programs are collected by individual states and collated at the national level by SAMHSA in DASIS (Drug and Alcohol Services Information Service or http://www.samhsa.gov/oas/dasis.htm, Office of Applied Statistics, n.d.). The usefulness of DASIS for monitoring abuse is limited because it does not cover all substance abuse programs, and does not report individual names of medications unless the state reports it. Unfortunately, only a few states collect this information.

Community-based surveys serve as another source of information on abused medications. National estimates of school-aged children use of drugs are obtained through Monitoring the Future (http://www.monitoringthefuture.org; Monitoring the Future, 2002), but the reports do not include a detailed listing of drugs abused. Some states and localities supplement the information by conducting their own surveys of school-aged children. States may also be able to provide information on number of school-aged children who are suspended for possession or sale of medications from their respective Department of Education.

The largest community-based survey is the National Household Survey on Drug Abuse (NHSDA or http://www.samhsa.gov/oas/nhsda.htm, Office of Applied Statistics, n.d.). Conducted since 1971, it currently surveys approximately 70,000 individuals aged 12 and older to derive national and state-level estimates on drug abuse for the civilian, non-institutional population. As mentioned at the beginning of the article, NHSDA has documented the non-medical use of prescription medications as a substantial problem. The current survey specifically asks about medication use without a prescription or only for the experience or feeling it caused. There are additional questions aimed at severity of misuse that may be used to assess need for services. The questions are repeated to cover different classes of
medications (i.e. analgesics, tranquilizers, stimulants and sedative/hypnotics). Prompts and photographs are shown of historically common medications by class. Misuse of new medications reported by respondents would be collected in an “other” category. Recently the NHSDA has added specific questions on Oxycontin in response to growing awareness of its abuse. Using NHSDA for monitoring abuse of a specific medication is limited by the questions asked and the time lag in fielding and reporting the results of the survey. In late 2002, summary data for 2001 was available on-line. In 2002, the NHSDA was renamed the National Survey on Drug Use and Health.

Emergence of prescription medication abuse may also be obtained from the Community Epidemiology Work Group (CEWG or http://www.nida.nih.gov/organization/CEWG/CEWGHome.html; National Institute on Drug Abuse, 2002) and Pulse Check (http://www.whitehousedrugpolicy.gov/publications/index.html; Office of National Drug Control Policy, 2002). The CEWG, sponsored by NIDA, meets semi-annually and reports on activities in their metropolitan area (or state). The participants rely on a variety of indicators, including those mentioned above, as well as street outreach and focus groups. Pulse Check, sponsored by Office on National Drug Control Policy, reports on emerging trends in 20 areas through key informant interviews conducted semi-annually with epidemiologists/ethnographers, law enforcement officials, and directors of treatment programs.

The last category of generalized surveillance systems in the US is the criminal justice system. The Drug Enforcement Agency and state police collect information covering illegal, fraudulent prescriptions, pharmacy thefts, illegal importation, and other illegal activities associated with abuse of medications. Their collection system, however, is aimed at prosecution and not monitoring national abuse trends. There is a system of monitoring results of urine toxicology of arrestees for major drugs of abuse (Arrestee Drug Abuse Monitoring Program or ADAM) that currently is operating 35 sites. States may also finance drug testing of juveniles at criminal justice intake. No system exists, to our knowledge, for specific prescribed medications. The National Drug Intelligence Center of the Department of Justice (http://www.usdoj.gov/ndic, US Department of Justice, 2002) established in 1993 also monitors emerging trends in drug abuse.

The surveillance systems discussed above are designed for widely used medications with very high level of abuse or serious and acute medical consequences and/or high economic value. Their sensitivity is unknown for detecting situations where the medication is less frequently abused, the medical consequences are less visible, the diversion is lower or emerging, or the exposure to the medication is limited. They also do not provide estimates of people exposed to the medications to use as denominators to compare rates across medications.

Two systems currently exist for monitoring the number of people exposed to medications. One system is operated by a for-profit company that samples activities at all legitimate retail outlets for medications (http://www.imshealth.com, IMS Health, 2002). The information is available for a customized fee that increases as the market volume and share increases. In late 2002, the fees ranged from $1500 to over $100 000. The other system is operated by the DEA and called ARCOS (Automation of Reports and Consolidated Orders System or http://www.deadiversion.usdoj.gov/arcos/index.html; Drug Enforcement Agency, 2002). In late 2002, the DEA homepage provided public data on volume sold to the retail level (for national, state and zip codes) of all Schedule II and some Schedule III medications for 1999. The public listing on the DEA homepage, however, is new and may be updated faster in the future.

The general surveillance systems described above have been improved for monitoring emerging prescription medication abuse but are still designed to capture commonly abused medications. To provide estimates to authorities for implementing timely risk management strategies for new medications where there is concern about abuse, the postmarketing strategy may need to be enhanced over these general systems. Such a system ideally should be national in scope yet sensitive enough to detect regional clusters and still be detailed enough to characterize the abuse so that interventions or risk management strategies can be tailored. It must provide usable and valid estimates of abuse on a timely basis. Importantly, it also must provide those estimates using a validated design with a comparator drug or historical data for interpretation of the results.

Two specific postmarketing surveillance systems have been used to date in the United States. We will first present their outline and then discuss their advantages and disadvantages. Both frameworks were approved by the FDA and financed by the manufacturer of the respective medication.

2. Surveillance of tramadol

The first specific surveillance system (Cicero et al., 1999) focused on tramadol HCL (Ultram), a centrally active analgesic with weak u-opioid receptor agonist affinity (Raffa et al., 1992). Based upon preclinical (cf. Villarreal and Seegers, 1968), clinical (cf. Arend et al., 1978), and postmarketing data from other countries, tramadol was introduced in the US as a non-scheduled medication in 1995. Approval, however, was contingent upon the development of a surveillance system, overseen
by an independent steering committee, to detect un-
extpectedly high levels of abuse. The “unexpectedly”
high levels of abuse were calculated from the level of
abuse observed in other countries (Keup, 1993).

The surveillance system consisted of systematic col-
collection and evaluation of reports of suspected abuse in
high-risk populations surveyed through a key informant
network of drug abuse specialists and all spontaneous
reports of abuse received through Medwatch. All Med-
watch reports suggestive of tramadol abuse were sent to
the steering committee for evaluation. The committee
provided special training to the employees of the
manufacturer who had direct contact with those report-
ing adverse events to ensure that as much information as
possible was gathered at the time of contact. Respon-
dent-specific questionnaires for collecting the informa-
tion were developed and implemented. The rationale
behind the specific questionnaires was to maximize the
type of information available from patients, pharmacists
and physicians.

The key informant network was composed of all 110
National Institute on Drug Abuse (NIDA) grantees who
were conducting epidemiological and treatment studies
of drug-abusing populations and 145 other drug abuse
experts (e.g. clinicians, treatment counselors, methadone
clinic directors). The latter group was identified by the
steering committee and recruited to participate in the
surveillance efforts because these individuals were
trained as substance abuse specialists and knowledge-
able about trends in their geographic region. Informants
were located in 44 states but concentrated in the major
cities on the Atlantic, Pacific and Gulf coasts.

A paper and electronic questionnaire (Table 1) was
sent quarterly to each of the key informants for comple-
tion. The informants additionally agreed to contact the chair of the steering committee if tramadol
use abuse occurred between quarterly reports. To
compensate their participation, the informants were
offered a payment for each completed questionnaire
and all follow-up information requested. In the first 7
years of operation, the response rate for this selected
network was 49% with no visible trend in lack of
compliance over time.

All reports (n = 932) from Medwatch and informants
were evaluated and classified according to DSM-IV
(Diagnostic and Statistical Manual, 4th edition) criteria
for substance abuse and dependence (American Psy-
chiatric Association, 1994). Only 30% of the positive,
possible or alleged reports could be definitely classified
as satisfying criteria for drug abuse or dependence,
highlighting the difficulty of obtaining complete and
definitive information. The reports rated as “withdra-
wal” were exclusively those in which no other signs or
symptoms of dependence or abuse occurred; otherwise
the report was rated as positive. These categories were
further subdivided into 13 categories to provide as much
descriptive information as possible. After a report was
classified, it was entered into a database for tracking.

These reports formed the numerator for the estimate
of abuse. The denominator was derived from sales of
tables with allowance for number of tablets per
prescription and percentage of prescriptions actually
sold to arrive at an estimate of the number of people
exposed to tramadol per month. No allowance was
made in the calculations for diversion, excessive dosages
or illegal importation.

In addition to these reports of abuse, the independent
steering committee tracked prescription and prescrip-
tion-filling of tramadol compared with other analgesics
by geographic area. This analysis could highlight
potential geographic hotspots for more detailed exami-
nation.

Based upon these data and in-depth follow-up, the
positive reports of abuse were concluded to be mostly
due to transient experimentation and were limited to a
few geographic areas. In some instances, it was deter-
mined that individuals with a history of substance abuse
had been prescribed tramadol by physicians who
believed it to be a safe, non-addictive analgesic. In those
instances, intervention strategies were implemented in a
timely effort to reduce this inappropriate use, including
sales force retraining.

The key informant network was one component of a
larger postmarketing framework for tramadol abuse.
Another component was a prospective study of health-
care workers enrolled in monitoring programs for
impaired health care professionals (Knisely et al.,
2002). Historically, health care professionals are
amongst the first defined population to experiment
and abuse prescription medications primarily due to
their knowledge about new medications and access. In
the case of tramadol, they may also be more likely to be
aware that the package insert lists a lack of urine
toxicology screen for the medication. The investigators
theorized that the combination of a novel pain analgesic
and lack of a toxicology screen would make tramadol

Table 1
Questionnaires used by the tramadol postmarketing program

<table>
<thead>
<tr>
<th>Please return by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quarter</td>
</tr>
<tr>
<td>Name</td>
</tr>
<tr>
<td>Study ID#</td>
</tr>
<tr>
<td>I wish — do not wish — to participate</td>
</tr>
<tr>
<td>In the past 3 months, have you had any reports in your study populations/patients/community of prescribed abuse or non-prescribed use/abuse of Ultram or Ultracet (37.5 mg of Ultram+32.5 mg of acetaminophen)?</td>
</tr>
<tr>
<td>Ultram — Yes — No — Do not Know —</td>
</tr>
<tr>
<td>Ultracet — Yes — No — Do not Know —</td>
</tr>
<tr>
<td>If your answer is yes, please fill out the enclosed questionnaire*</td>
</tr>
<tr>
<td>What is the population size you screen per month?</td>
</tr>
</tbody>
</table>

* Available in Appendix A
appealing to health care professionals who have identified substance abuse disorders and are required to have toxicology screens performed as part of a monitoring program. The investigators obtained the cooperation of four state-based health care professionals monitoring programs located in different regions of the United States. The programs agreed to send samples to a federally-approved laboratory for analysis, add standardized intake interviews, and perform follow-up interviews (including verification of prescription) for individuals indicated by the investigators. To avoid biasing the programs against people who tested positive for tramadol, the programs were also sent lists of individuals who tested negative for tramadol. More intensive measures were imposed for those individuals who continued to test positive for any substance and did not have a valid prescription. The investigators were thus able to document the rate of experimentation and continued use of tramadol, characteristics of the individuals testing positive for tramadol, and to compare the rate and characteristics of users with those of other medications. The findings corroborate the low rate of abuse found in the key informant study.

Other components of the postmarketing framework not discussed here include internet discussion and website monitoring, and a study focusing on chronic pain patients. The latter group was chosen as to assess the rate of abuse in populations exposed therapeutically to the medication but has not been published to date.

3. Surveillance of sibutramine

The second program for assessing abuse in a post-marketed medication monitored sibutramine (Arfken et al., 2003). Sibutramine (Meridia) was approved by the FDA for treatment of obesity in 1998. It is chemically related to amphetamine and appears to exert its action by blocking the reuptake of norepinephrine and serotonin, much like classic antidepressants (Buckett et al., 1988). In assessments of its abuse liability in animal (Heal et al., 1992) and human studies (Schuh et al., 2000), it did not share a profile of effects with amphetamine even at supra-therapeutic doses. Based upon its chemical structure, however, the FDA recommended that it be placed in Schedule IV (i.e. medical benefit with low abuse potential) but agreed to review postmarketing data. It is also one of the first scheduled medications with direct-to-consumer advertisement.

The sibutramine postmarketing program was based upon responses by individuals at high-risk for abuse or knowing about abuse. A single page anonymous questionnaire was added to the intake form of 58 community substance abuse treatment and university-based programs in the US. The programs approached for participation were selected to cover the geographic area of the continental US and different treatment modalities; they were not randomly selected or considered nationally representative. Unfortunately, they mirrored the results of the tramadol study by being concentrated on the Atlantic and Pacific coasts. The questionnaire asked six questions and collected limited demographic information (Table 2). The questions on awareness, use and misuse were asked in relationship to the medication of interest, sibutramine, and its marketed names. For a drug comparison, phentermine was selected as it is also a Schedule IV anorectic and has been marketed for decades with only low levels of abuse. In addition to the generic name, its marketed names were included. To assess the respondent’s likelihood to respond positively to any drug name, a fabricated name was included. It should be noted that the questionnaire did not ask the respondent about personal use but instead if they knew of anyone who might have used, including themselves. This was done in order to increase the perception of anonymity and cast a wider net for cases of abuse.

The initial protocol dictated that treatment programs included in the surveillance system were to obtain information from 100 respondents only over at least a 5-month-period. This component of the protocol was to limit by design the burden to treatment programs of participating. Total duration of data collection across all treatment programs was to be 1.5 years. Unanticipated problems in recruiting programs and the company’s desire to prolong data collection for an additional year resulted in modification of the initial protocol. Programs that were willing to extend the data collection and had received human ethics regulatory approval were encouraged to continue their data collection after they completed collection of the initial 100 respondents. Actual data collection was initiated November 1999 and concluded September 2001. Direct-to-consumer advertisements of sibutramine occurred between October and April in 1999, 2000 and 2001. Treatment programs were reimbursed for each completed questionnaire.

In contrast to the tramadol program, there was no a priori plan to derive national estimates of either misuse or abuse. Instead, comparisons were made between sibutramine and phentermine, and between sibutramine and the fabricated name. The expectations were 3-fold: (1) phentermine would have greater measurable levels of continued use to get high (a proxy for abuse) than sibutramine and (2) reports of hearing of the fabricated drug would be lower than for sibutramine. As the direct-to-consumer advertisements were aimed at women, it was expected that (3) women would be more likely than men to have heard of sibutramine. The latter hypothesis serves as an internal check on the validity of the findings.
The sibutramine postmarketing program found relative risk of abuse associated with sibutramine was lower than that associated with a known abused drug, one that itself is considered low risk despite decades of population exposure. The study also found identical rates of having heard of sibutramine and phentermine, but higher rates of awareness in women compared with men. The relatively high rate of hearing of sibutramine may have been due to the direct-to-consumer advertisement. Similar to the postmarketing program for tramadol, the program described above was only one study within a larger framework for assessing abuse that included internet monitoring.

4. Comparisons of the postmarketing programs for tramadol and sibutramine

The postmarketing programs for tramadol and sibutramine share similarities and differences. Both programs targeted the high-risk group of individuals with current substance abuse problems as opposed to the general population. Both programs were capable of proactively collecting and compiling timely data. Both programs geographically spanned the US and sought to collect data far from major cities. Both programs included arrangements for detailed follow-up upon detecting local epidemics of abuse. Both programs were designed to collect data over time, starting soon after US approval for marketing was obtained.

There are also important similarities in the limitations of the programs. Both programs encountered difficulty in accessing rural populations. Both programs reported cases based upon location of key informant or program and not based upon the source of medication or primary residence of the individual. Both programs encountered difficulties due to missing and vague information. The sibutramine program, for brevity,

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Table 2

Questionnaire used by the sibutramine postmarketing program

<table>
<thead>
<tr>
<th></th>
<th>FASTIN</th>
<th>MERIDIA</th>
<th>CATOREX</th>
<th>PHENTERMINE</th>
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<tbody>
<tr>
<td>(1) Have you ever heard of the following drugs?</td>
<td></td>
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<tr>
<td>IONAMIN</td>
<td>Yes No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADIPEX</td>
<td></td>
<td>Yes No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REDUCTIL</td>
<td></td>
<td></td>
<td>Yes No</td>
<td></td>
</tr>
<tr>
<td>SIBUTRAMINE</td>
<td></td>
<td></td>
<td></td>
<td>Yes No</td>
</tr>
</tbody>
</table>

| (2) Have you ever heard of the following drugs being sold on the street? |         |         |         |             |
| IONAMIN                | Yes No |        |        |             |
| ADIPEX                 |        | Yes No |        |             |
| REDUCTIL               |        |        | Yes No |             |
| SIBUTRAMINE            |        |        |        | Yes No      |

If YES to heard of the drugs being sold on the street in question #2, ask this question

| (3) How much did it cost? |         |         |         |             |
| IONAMIN                |        |        |        |             |
| ADIPEX                 |        |        |        |             |
| REDUCTIL               |        |        |        |             |
| SIBUTRAMINE            |        |        |        |             |

| (4) Do you know anyone, including yourself, who has used the following drugs to get high? |         |         |         |             |
| IONAMIN                | Yes No |        |        |             |
| ADIPEX                 |        | Yes No |        |             |
| REDUCTIL               |        |        | Yes No |             |
| SIBUTRAMINE            |        |        |        | Yes No      |

If YES to used any drug to get high in question #4, ask this question

| (5) Did they or you like it? |         |         |         |             |
| IONAMIN                |        |        |        |             |
| ADIPEX                 |        |        |        |             |
| REDUCTIL               |        |        |        |             |
| SIBUTRAMINE            |        |        |        |             |

If YES to used any drug to get high in question #4, ask this question

| (6) Did they or you use it again? |         |         |         |             |
| IONAMIN                |        |        |        |             |
| ADIPEX                 |        |        |        |             |
| REDUCTIL               |        |        |        |             |
| SIBUTRAMINE            |        |        |        |             |

sacrificed using the complete DSM-IV criteria for abuse and focused instead on repeated use to get high as a surrogate measure.

In addition to similarities in the design and the limitations of the programs, there are important similarities in the medications they studied. Preclinical and clinical behavioral studies concluded that both tramadol and sibutramine had low abuse liability. Neither medication roused much mass media interest. It is not known how these programs would have fared with a high profile medication.

The differences between the tramadol and sibutramine postmarketing surveillance programs are substantial. While the programs both targeted the drug abusing population, they differed on how they obtained information from them. The tramadol program relied upon key informants to report abuse; the sibutramine program queried individuals directly at the time of intake to substance abuse treatment. Thus, the sibutramine information was collected under a standardized protocol across programs and over time. The key informants may have queried individuals directly or may have relied upon passive collection of abuse data. The tramadol program empanelled the key informants at the initiation of the program. The sibutramine program initially only recruited treatment programs for 5 months of participation, complicating trend analysis. The sibutramine program also relied upon anonymous reports of abuse, precluding follow-up efforts with individual patients. Lastly, the definition of abuse differed between the programs.

By design, the tramadol and sibutramine programs had different priorities. The tramadol program had the objective of comparing national rates of abuse in the US to that experienced over decades in Germany. The sibutramine program did not have a priori knowledge of how the medication would be abused. It thus had the objective of comparing the rate of abuse for sibutramine relative to an already marketed medication for the same indication in the same schedule. The sibutramine program also had the objective of determining characteristics of the individuals reporting hearing of abuse. One of the key findings was the similarity in individuals (primary drug of abuse, geographic location) who reported hearing of sibutramine abuse and those who report hearing of phentermine abuse.

The surveillance programs also differed on the regulatory processes required for data collection. As the sibutramine program collected standardized information from individuals at high-risk for abuse, the treatment programs were required to obtain regulatory approval for data collection. In the tramadol program, if a key informant relied upon passive hearsay, no local regulatory approval may have been required. On the other hand, if the key informant actively questioned individuals, then local regulatory approval was required. This difference in regulatory requirement represented a major obstacle to recruiting treatment programs for the sibutramine program.

Lastly, the tramadol and sibutramine programs established surveillance on medications that were differentially scheduled. One, tramadol, was unscheduled and the manufacturer was motivated to keep it unscheduled. The other, sibutramine, was scheduled and the manufacturer was motivated to de-schedule it. It is not clear how the FDA reviews the results based upon the rationale for the study or what constitutes sufficient data for the FDA to take action to schedule versus de-schedule a medication.

5. Conclusions

These two postmarketing programs clearly demonstrate that surveillance programs can collect timely data allowing risk management strategies to be devised. The postmarketing findings validate the pre-marketing findings from abuse liability studies. The pre-marketing findings leading to conclusions of little abuse liability resulted, however, in different scheduling decisions for the two medications. The postmarketing programs do not meet the expectation of valid categorization of abuse by distinguishing abuse from misuse. The problem of missing or vague data represents a formidable barrier to arriving at clear answers. The programs can, however, clearly distinguish abuse as defined by DSM-IV from withdrawal symptoms.

Both programs reported low rates of abuse in agreement with the pre-marketing studies. It has yet to be proven that such postmarketing program designs will work when there is a problem with abuse of a medication. As such, the level and complexity of surveillance needed to detect abuse is not known. The programs both targeted substance abusing populations. If the medication is initially abused by other populations (and they do not seek treatment in the short-term), the initial postmarketing surveillance program may miss the abuse. The sibutramine program found people seeking treatment for stimulant abuse were more likely to have heard of people repeatedly using sibutramine (and phentermine) to get high than people who abused other classes of drugs. The developers of postmarketing surveillance programs should focus their efforts on populations believed to be most vulnerable to abuse and justify the focus. To provide guidance on interpretation (and internal validity on the program design), comparator medications should also be included. Information on number of people exposed to the medication and the comparator medications is highly valuable. Key informants, if used, should have active, ongoing knowledge of changes within the focused target populations.
The programs also demonstrated weakness in surveillance of rural areas. These low-density areas have a deficit of both treatment programs and key informants. In fact, treatment programs located in rural areas may draw their clientele from urban areas and, thus, not provide valid estimates of abuse in their areas. Other methods for detecting abuse in rural areas need to be developed.

Possible solutions to problems encountered with postmarketing surveillance include focusing on groups believed to be at high-risk but in a way that does not encourage illicit experimentation. This might be accomplished through surveillance of multiple medications simultaneously. It also could be facilitated by using reporting networks already in place. By using treatment programs and key informants with defined populations and experience in data collection, start-up time may be minimized and confidence in the findings enhanced. Manufacturers and investigators are also assured all regulatory steps are followed.

The importance of using of multiple methods of surveillance cannot be overemphasized. Even when a chosen method is based upon best available data and thoughtful review of prior experience, one single design may miss the target population or region where abuse is first localized. A tiered approach of detecting possible hotspots with further information provided by skilled ethnographers could optimize resources. Efficient mining of large databases, such as patterns of prescription filling and pharmacy orders, and use of general surveillance systems should also be included in specific postmarketing surveillance frameworks.

Finally, thought must be given to financing specific postmarketing surveillance for those drugs with promising therapeutic effects for a small number or economically disadvantaged group. The manufacturers underwrote the postmarketing programs discussed here. One medication targets chronic pain relief and is currently one of the top medicines prescribed in the US. The other medication targets weight loss and has an ever-expanding potential pool of patients. Other medications of concern may not enjoy those market potentials yet offer needed benefit. Alternative financing or on-going surveillance for multiple medications may be the only way to ensure abuse is identified on a timely basis. By having data on a timely basis, risk management strategies can be implemented (e.g. medications reformulated or scheduled, additional training for sales force, or warnings to physicians).

The field of postmarketing surveillance for abuse of prescription medications is in its infancy. More research is needed on the design, target population, appropriate comparisons, and timely acquisition of valid information on abuse in a context that does not encourage experimentation.

Acknowledgements

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Appendix A

Detailed questionnaire to be filled out if any abuse was detected

In the past 3 months have you had any new reports of prescribed abuse or non-prescribed use/abuse of Ultram (standard 50 mg tablet) or Ultracet (37.5 mg of Ultram + 32.5 mg of acetaminophen)? If yes, please list

Total number of cases you have heard about in the space provided below.

<table>
<thead>
<tr>
<th></th>
<th># of cases</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultram</td>
<td>Yes _______</td>
<td>No _______</td>
<td>Do not know</td>
<td></td>
</tr>
<tr>
<td>Ultracet</td>
<td>Yes _______</td>
<td>No _______</td>
<td>Do not know</td>
<td></td>
</tr>
</tbody>
</table>

Are you aware of any cases in which Ultram or Ultracet has emerged as a primary drug of abuse or drug of choice?

<table>
<thead>
<tr>
<th></th>
<th># of cases</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultram</td>
<td>Yes _______</td>
<td>No _______</td>
<td>Do not know</td>
<td></td>
</tr>
<tr>
<td>Ultracet</td>
<td>Yes _______</td>
<td>No _______</td>
<td>Do not know</td>
<td></td>
</tr>
</tbody>
</table>

In which population (e.g. methadone clients, others in treatment, street addicts, etc) and what was reported (specify product line)?

Are you aware of any instances in which Ultram or Ultracet are being abused in combination with other drugs to produce mood-altering effects or as a substitute for heroin or other drugs? Please provide the number of cases in the space below.

<table>
<thead>
<tr>
<th></th>
<th># of cases</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultram</td>
<td>Yes _______</td>
<td>No _______</td>
<td>Do not know</td>
<td></td>
</tr>
<tr>
<td>Ultracet</td>
<td>Yes _______</td>
<td>No _______</td>
<td>Do not know</td>
<td></td>
</tr>
</tbody>
</table>

In which population (e.g. methadone clients, others in treatment, street addicts, etc) and what was reported (specify product line)?
References


