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Physical dependence on Ultram® (tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur

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Abstract

In 1994, the Drug Abuse Advisory Committee (DAAC) of the Food and Drug Administration (FDA) concluded that Ultram® (tramadol hydrochloride) could be marketed as an analgesic drug without scheduling under the Controlled Substances Act based upon extensive pre-clinical, clinical and European epidemiological data. However, to guard against unexpectedly high levels of abuse in the United States, the DAAC recommended that an independent steering committee (ISC) be appointed to proactively monitor abuse/dependence. In the event that high rates of abuse were found, this ISC was given the authority to immediately recommend to the FDA that Ultram® be scheduled. In the course of the surveillance project, the ISC received reports of withdrawal following abrupt discontinuation of Ultram® and in some instances, following dose reductions. In most cases, the withdrawal symptoms consisted of classical opioid withdrawal, but in some cases were accompanied by withdrawal symptoms not normally observed in opiate withdrawal, such as hallucinations, paranoia, extreme anxiety, panic attacks, confusion and unusual sensory experiences such as numbness and tingling in one or more extremities. Withdrawal symptoms of either type were one of the more prevalent adverse events associated with chronic Ultram® use, comprising nearly 40% of all adverse events reported with Ultram®. Most of these consisted of typical opiate withdrawal symptoms, but 1 in 8 cases presented as atypical. These results indicate that physicians and other healthcare professionals need to be aware of the potential of Ultram® to induce withdrawal of the classical opioid type, and that atypical withdrawal may also occur.
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1. Introduction

In 1994, the Drug Abuse Advisory Committee (DAAC) of the Food and Drug Administration (FDA) recommended that Ultram®, containing a novel analgesic (tramadol hydrochloride) thought to act as a typical Mu-opioid agonist and with some analgesic activity mediated by non-opioid mechanisms (i.e. norepinephrine and serotonin reuptake inhibition (Raffa et al., 1992), be marketed without scheduling under the Controlled Substances Act (CSA). This decision was based primarily on, first, extensive pre-clinical and clinical evidence predicted a very low level abuse; and second, in 17 years on the market in Europe, abuse and dependence rates were very low. The DAAC was concerned, however, that unexpectedly high rates of abuse/dependence might emerge in this country. In response to this

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concern, the DAAC endorsed a recommendation that Ortho-McNeil Pharmaceuticals (OMP), the sponsor of Ultram®, establish an independent steering committee (ISC) to oversee a post-marketing surveillance program. The charge of the ISC was to develop mechanisms to proactively monitor for abuse/dependence as a means of providing an early warning signal that the drug might be found to have a higher rate of abuse and dependence in the American market than was expected. In an unprecedented step the company (OMP) agreed that, should the abuse of Ultram® be higher than expected, the ISC would simultaneously notify the FDA and OMP that Ultram® needed to be scheduled. The multi-faceted post-marketing surveillance program created by the ISC has been presented in detail in a prior publication; the rates of abuse and dependence from the launch of Ultram® in April of 1995 through June 30, 1998 were also presented (Cicero et al., 1999).

The ISC developed a two-tiered approach to detect whether Ultram® had unexpectedly high abuse potential. The first tier consisted of two phase IV post-marketing studies focusing on the potential abuse of Ultram® in pain patients and impaired health care professionals. The second tier consisted of a comprehensive, proactive surveillance program devised to detect any signal that abuse of Ultram® might be emerging. With respect to the latter, the ISC recognized that no systematic monitoring for abuse liability had ever been conducted for any newly approved psychoactive medication and thus, the surveillance program for Ultram® was unprecedented (Brewer and Colditz, 1999; Temple, 1999). The committee concluded that any surveillance program needed to incorporate the following critical elements: first, the program needed to be proactive and timely in soliciting evidence of Ultram® abuse; second, it had to be sensitive enough to detect isolated, regional clusters of abuse; third, methods needed to be developed to characterize the abuse permitting the development of intervention strategies; fourth, suspected cases of abuse needed to be validated utilizing scientifically appropriate diagnostic criteria; and finally, the program had to incorporate methods to estimate the number of patients exposed to Ultram® and hence, the rate of abuse to enable a risk-benefit analysis (i.e., cases of abuse per 100 000 patients exposed). While any adverse event, such as abuse or physical dependence is unfortunate, this risk must be balanced against the potential benefits of the drug; the rate of abuse provides such a measure.

The ISC recognized that the MedWatch system utilized by the FDA (Kessler, 1993) had a number of limitations as a proactive surveillance technique (Faich, 1986; Piazza-Hepp and Kennedy, 1995). First, the program significantly underestimates abuse since it relies upon spontaneous reports; second, the reports generally lack sufficient information for valid clinical assessments; and finally, the program primarily records events occurring in patients in whom abuse is expected to be very low and hence, probably understates the nature and scope of abuse. As a result of these limitations, the ISC developed a large national base of 'key informants' to proactively seek evidence of abuse in individuals at risk for abuse. The term 'key informants', which is borrowed from the fields of social and cultural anthropology (Agar, 1980), refers to clinicians, epidemiologists, treatment counselors, and other observers who are well recognized experts in the field of substance abuse and who are in a position to know about new and emerging drug problems in their areas. The informants provided information to the ISC at least quarterly, and each case was evaluated using the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV) criteria to determine whether abuse actually occurred. This comprehensive surveillance system (Cicero et al., 1999) provided proactive and timely information on abuse patterns stratified by postal zip codes across the country.

In earlier work, we have described in full the implementation of the surveillance program (Cicero et al., 1999) and presented the abuse rates and profiles of Ultram® during the first 3 years of marketing in the United States. In the present paper, we describe the characteristics and incidence of the withdrawal syndrome induced by abrupt cessation of chronic Ultram® use. In the course of the surveillance project, we received reports of withdrawal following abrupt discontinuation of Ultram® or, in some instances, following dose reductions in an established regimen of administration. Although the Ultram® label clearly warns of withdrawal upon abrupt discontinuation of chronic dosing, many physicians apparently did not heed this warning and abruptly stopped Ultram® therapy instead of tapering the dose as recommended. The withdrawal symptoms, in most cases, consisted of classical opioid withdrawal, as described in DSM-IV. In some cases, however, classical opioid withdrawal symptoms were accompanied by withdrawal symptoms not normally observed in opiate withdrawal, such as hallucinations, paranoia, extreme anxiety, panic attacks, confusion and unusual sensory experiences such as numbness and tingling in one or more extremities. The characteristics of the withdrawal syndrome—typical and atypical—for the 5-year period from the date of launch of Ultram® (April 1995 to March 2000) are presented in this paper.

2. Methods

2.1. IRB approval of the protocols

The Institutional Review Board (IRB) at Washington University approved the studies described in this paper;

Washington University was used as the primary site for the research since the chairman of the ISC (Theodore J. Cicero) was the PI for the grant and handled all aspects of mailing the questionnaires, securing additional information as needed and distilling the data.

2.2. Detailed methods

The ISC received reports of withdrawal from two sources. First, reports of suspected withdrawal and abuse generated by Ultram® were received by OMP from patients, pharmacists, physicians, and the FDA via the MedWatch system (Kessler, 1993). Second, the committee developed a large national base of 'key informants' to proactively seek evidence of abuse and withdrawal in individuals at risk for abuse. The network was composed of 110 National Institute on Drug Abuse (NIDA) grantees conducting comprehensive epidemiological and treatment outcome studies of drug-abusing populations, along with 145 other drug abuse experts identified by the ISC (e.g. clinicians, treatment counselors, methadone clinic directors). Collectively, the network provided access to approximately 250 000 at risk individuals. A questionnaire, jointly developed by the ISC and NIDA, was sent quarterly to the key informants, who also agreed to contact the Chairman of the ISC immediately if Ultram® abuse emerged in their populations between quarterly surveys. In all cases, when an informant indicated that a case of abuse had been detected, the Chairman obtained more information by direct contact.

The informants were offered a payment of $75 for each completed questionnaire and all follow-up information requested. In the 20 quarters covered by this report, the average response rate was 48.7%.

All reports, obtained from OMP, the FDA and those proactively elicited by the committee were evaluated and classified by a sub-committee of the ISC according to DSM-IV criteria for substance abuse and dependence and withdrawal. The scoring system is shown in Table 1. The chairman (Theodore J. Cicero) also transmitted these reports to OMP so that they could be sent to the FDA via the MedWatch system each calendar quarter. Thus, the FDA received adverse event reports (MedWatch reports) within 3 months of their occurrence.

The reports were classified by the sub-committee as either positive, possible, alleged or negative for abuse or as withdrawal (Cicero et al., 1999), see Table 1. In this classification system, a clear distinction was made between the occurrence of withdrawal symptoms alone and withdrawal symptoms accompanied by drug-seeking behavior. This distinction was important for two reasons. First, withdrawal symptoms occur with many substances (e.g. tricyclic antidepressants, beta blockers, etc); in most cases these withdrawal symptoms are not associated with signs or symptoms of drug abuse; second, it was recognized that drug-seeking behavior may be motivated, to some extent, by relief of withdrawal symptoms and hence, the ISC believed that when withdrawal and drug-seeking behavior were both present the case should be classified as abuse (rating 10–14, 20 and 30, Table 1), not withdrawal. A withdrawal rating was used only when there was no other evidence of abuse.

Table 1
ISC ratings

ISC rating	ISC subcategory	Description
Positive	10	Satisfies DSM-IV criteria for drug dependence.
	11	Satisfies DSM-IV criteria for drug abuse.
	12	Physician reports drug abuse or dependence, not clear that DSM-IV criteria were met.
	13	Ultram® intentionally used to produce euphoria, euphoria occurred.
	14	Ultram® intentionally used to produce euphoria in combination with other drugs, euphoria occurred.
Possible	20	DSM-IV criteria for drug dependence partially met, but no definitive diagnosis.
Withdrawal	21	Typical opioid-like withdrawal upon discontinuation of Ultram® (no indication of abuse).
	22	Atypical opioid-like withdrawal upon discontinuation of Ultram® (no indication of abuse).
Alleged	30	Suspected abuse/dependence, insufficient information to draw definitive conclusion.
Negative	31	Euphoria/high occurred after therapeutic use of Ultram®, no other signs of abuse/dependence.
	40	No evidence of abuse, dependence, or euphoria.
	41	Drug experienced person tried Ultram® to get high, reports lack of success.
	42	Drug experienced person tried Ultram® with other drugs to get high, reports lack of success.

During the course of the study, the ISC noted that withdrawal from Ultram® was usually typical for opioid drugs. As the study progressed, however, we encountered adverse events of classical opioid withdrawal accompanied by unusual symptoms such as hallucinations, paranoia, extreme anxiety, panic attacks, confusion and unusual sensory experiences such as numbness and tingling in one or more extremities. Thus, for the data presented in this paper, the ISC rescored all of the withdrawal cases for the 5-year period from 1995–2000 as either typical or atypical withdrawal using the criteria shown in Table 1. The term 'atypical withdrawal' is not

necessarily meant to suggest that there are two distinct withdrawal syndromes seen with Ultram®, but merely serves as a descriptor to differentiate typical opioid withdrawal symptoms—most commonly seen with Ultram®—from the occurrence of atypical opioid withdrawal and the unusual symptoms just described.

2.3. Estimation of patient exposure and rates of abuse

Since the number of cases of withdrawal alone does not give any indication of the frequency of withdrawal in patients exposed to Ultram®, the ISC determined that the rate of withdrawal, expressed as the number of patients experiencing withdrawal per 100 000 patients prescribed the drug, needed to be determined. To accomplish this, the ISC developed an algorithm, which permitted an estimate of patients exposed to Ultram® in a given month. This algorithm has been described fully elsewhere (Cicero et al., 1999), but consisted of several critical elements: the number of tablets manufactured each month, the number sold and the average prescription size. From these data, the number of patients for which Ultram® had been prescribed was determined. Once this denominator was available, the rate per month of withdrawal—typical or atypical—was determined by dividing the actual number of cases received by the number of patients exposed in that month and quarter.

2.4. Management of withdrawal from Ultram®

The ISC members also offered advise to physicians in the field who called OMP asking for assistance with the management of withdrawal and/or abuse/dependence following cessation of chronic Ultram® treatment. Clinicians from the ISC carried out approximately 75 such consultations. From these personal contacts, the ISC was able to obtain a great deal of information about the characteristics of the withdrawal syndrome and most importantly, its clinical management.

3. Results

3.1. Characteristics of Ultram® withdrawal

Table 2 shows the signs and symptoms of typical ($N = 367$) and atypical ($N = 55$) withdrawal from Ultram® (total = 422). The incidence of specific atypical withdrawal symptoms occurring in patients diagnosed with atypical withdrawal is given as a percent of total atypical cases showing the respective symptoms. According to DSM-IV criteria at least three of the symptoms of typical opioid withdrawal listed in this table were necessary for a classification of typical opioid withdrawal or physical dependence; thus all of the patients exhibited at least 3 of the symptoms listed to score as a typical opioid withdrawal syndrome. The primary distinction between typical and atypical withdrawal is that atypical withdrawal, while it was always accompanied by many symptoms associated with typical withdrawal, also had a strong component of other CNS disturbances not usually observed in typical opioid withdrawal. These CNS disturbances included intense anxiety and panic attacks (nearly one-third of the patients), unusual CNS symptoms such as confusion, delusional behavior and derealization, unusual sensory phenomena (e.g. numbness, parathesia, and tinnitus, tingling in the extremities) and hallucinations, tactile, visual and auditory.

Table 2
Features and symptoms of typical and atypical withdrawal from Ultram®

Typical opioid withdrawal[a] ($N = 367$)	Atypical withdrawal[b] ($N = 55$)	% Frequency[c]
Abdominal cramps Anxiety	Severe anxiety and panic attacks	32.8
Bone pain Depression Diarrhea Goose flesh Insomnia Lacrimation Nausea	Unusual CNS symptoms Confusion Delusions Depersonalization Derealization Paranoia	27.2
Restlessness Rhinorhea Sweating	Unusual sensory phenomena Numbness Tingling Parathesia Tinnitus	25.4
	Hallucinations Tactile Visual Auditory	20.0

[a] DSM-IV requires that 3 or more of these symptoms are present to meet the definition ofwithdrawal or physical dependence.
[b] Often combined with typical opioid withdrawal signs and symptoms. Listed in order of decreasing prevalence.
[c] Total adds to more than 100% since multiple signs were frequently reported.

From the launch of Ultram® in April of 1995 through March 2000, 422 cases of opiate withdrawal (367 and 55 for typical and atypical, respectively) were observed which accounted for 33% of all adverse events reported (Table 3). As can be seen from Table 3 and Fig. 1, most withdrawal cases were rated as typical opioid withdrawal ($\cong 87\%$), while 1 in 8 was atypical. As shown in Fig. 1, there was evidence of typical and atypical withdrawal cases immediately after the launch of Ultram®; total withdrawal cases reached a rate of 2.5–3.0 cases/100 000 patients 12–15 months after the launch of Ultram®. The rates have since declined to a rate of less than 1 case per 100 000.

Table 3
ISC rated withdrawal cases April 5, 1995 to March 31, 2000

	Number of cases ($N = 422$)	% of all withdrawal cases	% of total adverse events ($N = 1248$)
Typical	367	86.97	29
Atypical	55	13.03	4
Total	422	100.00	33

During the course of these studies 1248 adverse events were received and classified by the ISC. Of these, 422 (33%) were rated as typical or atypical withdrawal.

3.2. Incidence of typical and atypical withdrawal in cases rated as positive for abuse

As mentioned in the methods, withdrawal ratings were confined to only those cases in which no drug-seeking behavior was observed. If drug-seeking behavior was observed, the 'default' position imposed by the ISC was to rate the case as abuse even if some withdrawal symptoms existed. To better understand the true incidence of withdrawal in our subject population, however, the incidence of typical and atypical withdrawal symptoms in those rated as positive, possible or alleged abuse was also examined. We found that of the 644 cases of abuse, typical and atypical opioid withdrawal symptoms were present in 121 and 3 cases, respectively. Thus, the total number of withdrawal cases was at least 546 in this study.

3.3. Age, sex, history and Ultram®—induced withdrawal

We had access to age data for only 139 of 455 cases of withdrawal. Nevertheless, the distribution of the ages for the cases for which we have data appears to indicate that age is not an important predisposing factor in the phenomenon of Ultram®—induced withdrawal. We had data related to sex in 82% of cases with typical withdrawal and 87% in the cases of atypical withdrawal. In both instances, approximately 56% occurred in females (55.8 and 56.3 for typical and atypical, respectively). These data suggest that both typical and atypical withdrawal may be more common in females than in males, but the data do not appear to establish any relationship between sex and the occurrence of atypical or typical opiate-induced withdrawal.

3.4. Length of exposure, dose and Ultram®—induced withdrawal

We had data regarding length of exposure in approximately 50% of the cases of withdrawal. The length of exposure and the occurrence of typical and atypical withdrawal indicated that length of exposure was a weak variable in the withdrawal syndrome induced by Ultram®. There were many cases with relatively brief exposures (3–4 days) and no clustering in cases with extended exposure. We had information on maintenance dose in 63% of cases of typical withdrawal. The range was 50–2000 mg per day; the vast majority of withdrawal cases (92%) occurred at or below the maximal recommended therapeutic level of 400 mg per day. We

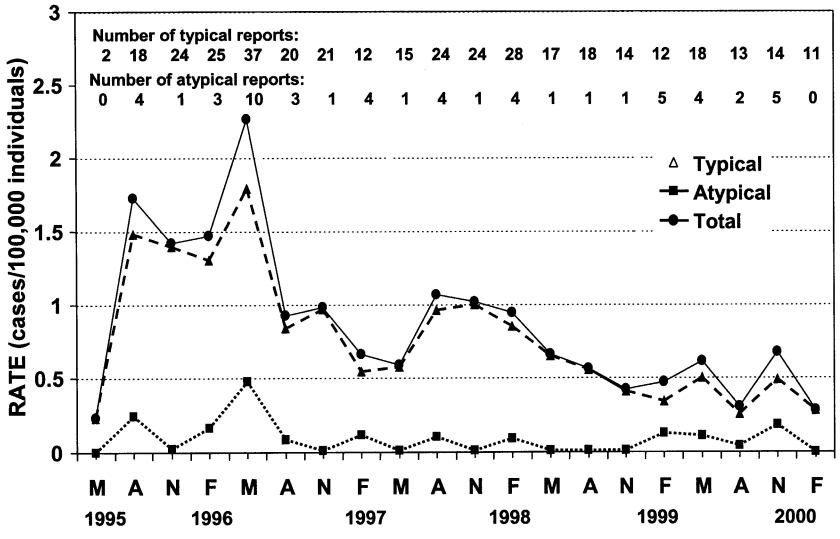

Fig. 1. The number and rate (cases/100 000 patients exposed) total, of typical and atypical withdrawal by quarters from 1995–2000. The month shown represents the middle month in each calendar quarter.

had information on dose in 78% of the atypical cases. The range for the atypical group was 50–1300 mg per day. In contrast to the results observed in the typical cases, 25% of all atypical cases occurred in patients using greater than the 400 mg per day recommended therapeutic level—three times higher than that observed with typical withdrawal (8%). Atypical withdrawal cases also tended to last longer and to be more troublesome in their clinical management than the typical cases.

3.5. Management of Ultram®—induced withdrawal

As reports came in from clinicians, we noted that many physicians failed to heed the warning on the label that Ultram® was capable of producing withdrawal and hence, the dose should be tapered. Thus many physicians abruptly stopped Ultram® therapy and not unexpectedly, withdrawal ensued. However, even in some cases in which the dose was tapered a withdrawal syndrome was observed. In either event, most physicians described patients with relatively mild cases of withdrawal and consequently, they simply monitored but did not treat the withdrawal symptoms. The problem usually resolved itself in 2 or 3 days. As the severity of the withdrawal syndrome increased, however, it was often necessary to treat the symptoms. For example, some reinstituted therapeutic dose levels of Ultram® and then tapered the dose very slowly; others stopped Ultram® use completely and used benzodiazepines, e.g., lorazepam, alprazolam and diazepam in low doses to treat the atypical withdrawal symptoms. Most of the atypical withdrawal symptoms responded well to benzodiazepines and/or to slow tapering.

4. Discussion

The results of these studies indicate that physicians and other healthcare professionals need to be aware of the potential for chronic Ultram® use to induce withdrawal of the classical opioid type upon abrupt cessation and sometimes even when the dose was tapered as recommended on the label. However, our results also clearly show that 1 in 8 Ultram® withdrawal cases presented as a mixture of classical opioid withdrawal with unusual features such as intense anxiety, depersonalization, delusions, confusion, hallucinations and other symptoms. Without this awareness, there is a distinct possibility of misdiagnosing these symptoms as a psychosis or delirium. Because Ultram® binds weakly to the Mu-opioid receptor, it was anticipated that patients would exhibit signs and symptoms of opioid withdrawal if chronic use of Ultram® was stopped. This did indeed occur, but as reports of Ultram® withdrawal were received, it became obvious that signs and symptoms different than classical opiate withdrawal were being reported in addition to, or in place of the expected typical signs and symptoms of withdrawal. These were more similar to withdrawal symptoms reported in withdrawal from SSRI antidepressants (Lejoyeux and Ades, 1997) than from opioids. These withdrawal signs and symptoms may be related to Ultram®'s reported mechanism of action as a norepinephrine and serotonin reuptake inhibitor (Raffa et al., 1992), but this remains to be determined. Nevertheless, the present data indicate quite clearly that typical opioid withdrawal symptoms occur with some frequency in patients in which Ultram® therapy is abruptly stopped, and in some of them unusual withdrawal symptoms may occur in addition to, or in place of, typical opioid withdrawal. Although the Ultram® label clearly indicates the possibility of typical (but not atypical) withdrawal, it is perplexing and disturbing that many physicians did not heed, or perhaps read this warning and taper the dose regimen. The results described in this paper underscore the need to taper the dose and that atypical withdrawal may also occur and need to be treated.

As mentioned in the results section, we observed a rate of withdrawal—both typical and atypical—of approximately 1 case per 100 000 patients exposed. While this rate is quite low, it is important to stress that withdrawal is, nevertheless, a clinically significant event and represented the most prevalent adverse events observed with Ultram® (nearly 40% of total cases). Furthermore, withdrawal was also a prominent and common feature of a large number of individuals rated as positive for Ultram® abuse. Hence, these observations collectively suggest that withdrawal—typical and atypical—is not an uncommon event when Ultram® use/abuse is abruptly discontinued and could serve as a factor leading to potential abuse. Physicians need to be aware of this possibility and manage it by gradual dose reduction and treatment with low dose benzodiazepines in the case of atypical withdrawal. Furthermore, since withdrawal could be one of the factors leading to abuse, physicians need to be vigilant for any signs or symptoms of abuse or dependence in their patient populations.

It is unclear why we found that the frequency of typical to atypical withdrawal was 7 to 1. These data would suggest that a relatively small number of patients are susceptible to the atypical withdrawal symptoms we observed. We found no difference in age, sex, length of exposure, or history of drug abuse in patients experiencing typical and atypical withdrawal and as a result, we are unable to define any features of patients that would help indicate who may be at risk for atypical withdrawal with one possible exception. A larger number of patients experiencing atypical withdrawal were at dose levels above the 400 mg suggested daily dose than those experiencing typical withdrawal (25% and 8%, respectively). It would seem prudent, therefore, for clinicians to be aware of the possibility of atypical withdrawal for

patients in whom therapeutic doses exceed 400 mg/day and adjust their treatment accordingly.

The ISC decided to use DSM-IV principles and criteria as the base of its adverse event rating system for reports of abuse, dependence and withdrawal. This would make our findings compatible with those of modern epidemiological and clinical research. The phenomenon of withdrawal without drug-seeking behavior does not have an established and widely accepted term to define it. Two terms have appeared in the literature. The first, 'neuroadaptation' (Edwards et al., 1981) has been used chiefly to describe withdrawal from opioids which emphasizes that physical dependence and its expression as a withdrawal syndrome reflect intrinsic drug-induced changes in neuronal function. The second, 'discontinuation syndrome,' describes withdrawal from an array of drugs and tends to reflect mainly the signs and symptoms of withdrawal without regard to the mechanisms involved. Both terms appear to be represented adequately by the DSM-IV term 'Drug-Induced Disorder' which, paraphrasing DSM-IV, means that there is a withdrawal syndrome without drug-seeking behavior, causing distress or impairment, and needing medical monitoring or active intervention without drug-seeking behavior.

The distinction between a 'Drug-Induced Disorder' of withdrawal and a 'Drug Use Disorder' of abuse or dependence is critical in assessing the public health impact of a drug like Ultram®. A 'Drug-Induced Disorder' of withdrawal occurs with many classes of drugs, e.g., antidepressants (Dilsaver, 1994; Einbinder, 1995; Lejoyeux and Ades, 1997), anti-psychotics (Gilbert et al., 1995), anti-hypertensives (Hart and Anderson, 1981; Houston, 1981), steroids (Yesalis et al., 1990) and others (Fishbain et al., 1988), but is rarely associated with abuse or dependence. On the other hand, a 'Drug Use Disorder' is characterized by dependence or abuse with or without withdrawal. Based upon this distinction, what we observed in this study with Ultram® was a 'drug-induced disorder' which bears little relationship to abuse or dependence. For example, we found that in all cases rated as withdrawal only, withdrawal was not associated with drug-seeking behavior; this syndrome, therefore, is clearly an example of a 'drug-induced disorder', not a drug use disorder. In fact, any cases of withdrawal in which we found evidence of abuse, as well as typical or atypical withdrawal, were classified by us as a 'drug use disorder' and scored as abuse or dependence. The distinction is critical since withdrawal in the absence of drug-seeking behavior, (i.e. a drug-induced disorder) has little or no relationship to abuse of the drug and should consequently be of little public health concern relative to abuse liability.

In this connection, the CSA requires that 'physical dependence' be monitored as evidence of abuse and the FDA therefore considers withdrawal—either as a drug induced disorder or a drug use disorder—to be one of the defining features of abuse/dependence on drugs. Since it is clear that withdrawal, in the absence of any other signs of drug-seeking behavior does not necessarily constitute abuse or dependence, it is clearly inappropriate to consider withdrawal alone as evidence of abuse or dependence.

Perhaps the most important aspect of the current report and our earlier publication dealing with abuse patterns (Cicero et al., 1999) is the nature and scope of the comprehensive post-marketing surveillance that was developed by the ISC. The need for post-marketing or risk management studies with most drugs is now clearly recognized by drug manufacturers and the FDA (e.g. see the web site for the CDER—Center for Drug Evaluation and Research—of the FDA) for a number of reasons. For example, very rare side effects may not be observed in relatively small clinical trials in which a few thousand patients may be utilized. In addition, there are limitations to the type of clinical studies normally carried out, and once again the sample sizes do not permit an assessment of true rates of abuse or withdrawal that might be observed after widespread exposure to the general population or those at risk for abuse. Indeed, we have found that Ultram® abuse (Cicero et al., 1999) occurred at a frequency of 1–1.5 cases/100 000 patients, and in the current paper withdrawal at less than 2 cases/100 000 patients. Neither of these events would have been detected in the typical clinical trial and in fact, in the case of Ultram®, phase I–III clinical trials involving approximately 5000 individuals did not suggest that either drug abuse or withdrawal would be a feature of this drug. Thus, in the case of Ultram®, the proactive post-marketing surveillance efforts have provided a great deal of real life, epidemiological data to better define its safety profile and abuse/withdrawal patterns. By extension, it seems obvious that, as has been suggested (Brewer and Colditz, 1999; Temple, 1999), proactive post-marketing studies would be appropriate for all drugs to obtain timely and clinically validated evidence of unsuspected adverse events, including, but not limited to substance abuse.

The latter conclusion is strengthened by the fact that a reliance on spontaneous reports, which is the backbone of the MedWatch System and Drug Abuse Warning Network, grossly underestimates the incidence of adverse events by the very nature of these reporting systems (Faich, 1986; Piazza-Hepp and Kennedy, 1995), no doubt because they are passive, retrospective and often anecdotal. The extent of under-reporting is not known, but the FDA estimates that spontaneous reports probably reflect only about 10% of the actual incidence of adverse events in the general population (Kessler, 1993). Furthermore, spontaneous reports drop over time (Brewer and Colditz, 1999; Temple, 1999) as a natural progression, since, as the nature of adverse

events become well known, they are reported with much less frequency. Thus, after several years, spontaneous reports probably reflect considerably less than 5% of the actual cases. Proactive surveillance efforts can overcome some of these difficulties, as was demonstrated in our earlier work (Cicero et al., 1999) in which we found that abuse was still being reported by an informant network well after spontaneous reports had declined to very low levels. Thus, although proactive surveillance efforts may not reveal the actual rates of abuse in the general population of millions, these approaches are certainly more accurate and clinically useful than spontaneous reports alone. Furthermore, and perhaps of even more significance, proactive surveillance techniques can provide a very timely signal that abuse may be emerging. For example, in the post-marketing surveillance program utilized for Ultram®, the FDA received reports at quarterly intervals and hence, they were aware of proactively obtained adverse events within 3 months of their occurrence. This permits the FDA to make 'real time' decisions well before a problem evolves into an epidemic, which may not be evident utilizing existing passive reporting systems.

Finally, a proactive post-marketing surveillance system provides a much more timely signal that an adverse event has occurred than if the spontaneous reporting systems currently available were used as the only source of information. For example, data from DAWN are published only after an 18–24 month publication delay and drug company generated MedWatch forms may not be received for 12 or more months. Thus, a reliance on DAWN and other passive surveillance systems does not provide a foundation for the timely indication that an adverse event, which might not have been detected in clinical trials has become a public health problem. Proactive post-marketing surveillance programs would seem to be one of the only means by which the incidence of adverse events can become more clearly evident at the earliest possible time.

The post-marketing surveillance program outlined in this paper was motivated by the FDA's requirement for a risk-benefit management or post-marketing surveillance study. As such, it might be concluded that the program for Ultram® is unique to the United States and therefore has little relevance for abuse in other countries. The ISC believes that this conclusion is wrong and that this type of post-marketing surveillance program could be easily expanded to cover many drugs of abuse wherever the drugs are marketed. Although it could be argued that many countries, especially in Europe, already have systems in place to monitor adverse events (e.g. the Upsala Monitoring Centre, the Prescription Events Monitoring Program used in the United Kingdom, The Center for Adverse Reactions in New Zealand), all of them suffer from the same problems as the DAWN and MedWatch programs in the United States. They are essentially passive, vary substantially in the definition of abuse—if this is monitored at all—and do not provide a timely signal that drug abuse may be a potential problem affecting public health until it has reached epidemic proportions. Therefore, a proactive surveillance program, such as that described in this paper, focusing specifically on abuse would complement and substantially extend the utility of existing systems and provide much more timely and accurate assessment of the abuse profile of new and established drugs worldwide.

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