Published in final edited form as:

Drug Alcohol Depend. 2009 December 1; 105(Suppl 1): S65–S71. doi:10.1016/j.drugalcdep.2009.08.006.

Risk Management Post-Marketing Surveillance for the Abuse of Medications Acting on the Central Nervous System: Expert Panel Report

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Contributors

Author CEJ wrote the original draft of the manuscript. With the input of RLB, JEH and CRS, a penultimate draft was finalized and sent to the other panel members. Each panel member reviewed the draft and suggested revisions. The final draft was completed by CEJ, RLB, JEH and CRS.

No Revision Notes Exist for this Manuscript

Abstract

The abuse and diversion of medications is a significant public health problem. This paper is part of a supplemental issue of *Drug and Alcohol Dependence* focused on the development of risk management plans and post-marketing surveillance related to minimizing this problem. The issue is based on a conference that was held in October, 2008. An Expert Panel was formed to provide a summary of the conclusions and recommendations that emerged from the meeting involving drug abuse experts, regulators and other government agencies, pharmaceutical companies and professional and other non-governmental organizations. This paper provides a written report of this Expert Panel. Eleven conclusions and eleven recommendations emerged concerning the state of the art of this field of research, the regulatory and public health implications and recommendations for future directions. It is concluded that special surveillance tools are needed to detect the emergence of medication abuse in a timely manner and that risk management tools can be implemented to increase the benefit to risk ratio. The scientific basis for both the surveillance and risk management tools is in its infancy, yet progress needs to be made. It is also important that the unintended consequences of increased regulation and the imposition of risk management plans be minimized.

Keywords

Prescription drug abuse; regulation; epidemiology; policy; pharmacovigilance; abuse liability; risk management; surveillance

1. Background and Definitions

This paper is part of a supplemental issue of *Drug and Alcohol Dependence* that summarizes the proceedings of a meeting on Risk Management and Post Marketing Surveillance of CNS Drugs sponsored by the College on Problems of Drug Dependence. As defined by the U.S. Food and Drug Administration (FDA), “risk management is an iterative process designed to optimize the benefit-risk balance for regulated products” (FDA, 2005; see also Leiderman, 2009; Scholl et al., 2006). In recent years, risk management has come to mean the pre and post drug approval strategies intended to maximize benefits and minimize risks *throughout the life-cycle* of a drug on the market and is not limited to just the initial approval and labeling. Three major components have been delineated by FDA and are described in FDA industry guidance documents (FDA, 2005a, 2005b, 2005c). These are (1) systematic evaluation of the nature, frequency and severity of potential risks of a drug; (2) implementation of a program of specific tools to minimize identified risks, referred to as *risk minimization action plan* or RISKMap; (3) post marketing surveillance to assess potential unintended consequences and thereby to enable interventions to minimize such consequences. A risk management program (RMP), therefore, is a comprehensive program of risk detection, assessment, mitigation, and intervention intended to improve the benefit-risk balance of a drug throughout its life cycle.

For the CPDD conference and this report, the expression “risk management” refers to both the risk management program approach described in the 2005 FDA guidance documents as well as the congressionally authorized approach referred to as *Risk Evaluation and Mitigation Strategy* (REMS), which has been increasingly extended to drugs since the conference was convened in October 2008. For example, in the spring of 2009, FDA proposed that REMS would be required to cover 16 extended release opioids and methadone (FDA, 2009).

Two additional regulatory tools used to contribute to the benefit-risk ratio may be considered risk management approaches. They were discussed in the conference but were not the focus of this Expert Panel Report. The first is drug scheduling, which occurs under the provisions of the Controlled Substances Act (CSA). This regulatory approach categorizes drugs in a

hierarchical manner according to their relative drug abuse risk and regulates access and marketing based on an assessment of its abuse potential (Drug Enforcement Administration, 2009; Spillane and McAllister, 2003; Schnoll et al., 2006). The assessment of the nature and severity of abuse risks that guide scheduling determinations is accomplished in part through an analysis of eight factors related to the drug's pharmacology, abuse liability, and public health risks. The second regulatory tool is FDA's Subpart H mechanism for enabling access to a drug only under highly restricted conditions (FDA, 2009).

2. Description of the process used to develop the conclusions and recommendations

The CPDD convened its meeting on Risk Management and Post Marketing Surveillance of CNS Drugs in Bethesda, Maryland in October 2008 (Schuster et al., 2009). This was the fourth in a series of drug abuse conferences sponsored by CPDD. Reports from two of these meetings already have been published in *Drug and Alcohol Dependence*, and both summarize meeting highlights as well as provide suggestions for future developments in addressing drug abuse risks (Johanson et al, 2003; Sellers and Johanson, 2006). As was true for the prior meetings, the October 2008 conference was attended primarily by representatives of four groups concerned with the issues of risk management and post marketing surveillance for the detection of diversion and abuse of CNS active drugs: (1) experts from academia and research institutions who are engaged in relevant research activities; (2) representatives from United States government agencies charged with developing and implementing policies as well as funding research that, *inter alia*, minimizes drug abuse risks; (3) pharmaceutical companies that develop and market CNS active drugs; and (4) professional and nongovernmental organizations concerned about the impact of risk management programs on the availability of drugs for legitimate medical purposes. To facilitate discussion among such a diverse group of stakeholders, the audience was limited to approximately 100 participants.

Prior to the meeting, the CPDD organizing committee identified the most relevant topics and commissioned experts to prepare four background papers that were distributed to participants. Subsequently, the October 2008 CPDD conference was organized around these four background papers as well as four case study presentations that highlighted risk management plans developed by pharmaceutical companies for recently approved medications. The background papers and a paper summarizing the case study presentations were peer-reviewed and edited for this supplemental issue (Leiderman, 2009; Carter and Griffiths, 2009; Dart, 2009; Dasgupta and Schnoll, 2009; McCormick et al 2009). At the meeting, the authors of all these papers were asked to give a summary presentation. These presentations formed the basis for the discussions among the participants leading to the conclusions and recommendations by the Expert Panel. Recommendations included statements of research needs. These were developed according to a protocol used in the prior meetings. After the first day's proceedings, the Expert Panel met and drafted conclusions and recommendations that were presented to the conference participants on the following morning. After the participants had an opportunity to discuss and offer amendments to the panel's report, the Expert Panel finalized its conclusions and recommendations in a report presented to the conference participants during the concluding session of the conference. This report formed the basis for the present article that has been reviewed by all members of the Expert Panel. The conclusions and recommendations of the Expert Panel presented here should not be construed as being a consensus statement of all participants in the conference. Rather, it represents the intent of the Expert Panel to summarize the most important conclusions and recommendations generally accepted by conference participants. It is hoped that the conclusions and recommendations reached by the Expert Panel will stimulate further thinking about unresolved issues and serve as a stimulus for additional

research that will validate the methods of risk management and post marketing surveillance proposed by conference participants.

3. Conclusions

3.1 Preclinical and human abuse liability laboratory-based testing has been shown to have good predictive ability for real world abuse of CNS active medications

Laboratory-based methods for assessing abuse liability are well established (Ator and Griffiths, 2003; Balster and Bigelow, 2003; Carter and Griffiths, 2009; Griffiths et al, 2003). In addition, clinical trials, if properly designed prospectively, also can provide useful information about abuse liability (Brady et al., 2003). With the development of new molecular targets and formulations of CNS active medications, traditional animal and human abuse liability testing methods may need to be modified (e.g., McColl and Sellers, 2006) if they are to serve as the basis for identifying novel drugs that should be controlled under the Controlled Substances Act (CSA), or other national or international regulatory schemes, as well as those needing additional risk management strategies. Besides the composition of the drugs themselves, there are exogenous factors in the post-marketing environment that may alter the extent to which abuse potential becomes reality. For instance, the potential abuse of a medication with known abuse liability may be greatly lessened if the medication is used only in hospital settings. Having a relatively high cost and being in a market occupied by less expensive alternative drugs with similar abuse liability may also prevent a medication's actual abuse. Given the many factors that may influence the actual abuse of a drug in the market place, abuse cannot always be predicted with accuracy. Nevertheless, until a drug is marketed, laboratory studies are the best available indicators of potential abuse and for formulating risk management and surveillance strategies. Using information obtained from preclinical and clinical laboratory-based studies, preliminary and reasonably accurate estimates of abuse and diversion can be determined. These estimates, in turn, may serve as a basis for the development of a plan to manage these risks.

3.2 The labeling for new drugs is the foundation for risk management

Currently, prescribing instructions, indications, and warnings of risks, including the risk of abuse and dependency, are included in every drug's FDA-approved label. The information is intended to provide information about the appropriate use of the drug as well as to alert physicians and patients about their side effects and risks, including the risk of abuse. However, in some cases, additional "tools" or "strategies," in the form of scheduling under the CSA, or, perhaps a formal REMS, may be warranted to address and mitigate abuse risks.

3.3 Scheduling of a drug under the Controlled Substances Act (CSA) is an approach to risk management that goes beyond labeling, but is not considered a substitute for risk management programs or REMS

The concept of drug scheduling was initially devised to provide a formal system of controls that are proportional and appropriate to the abuse-related risks posed by a drug that has been shown to be medically useful, based on an acceptable benefit to risk ratio. The formal scheduling process in the U.S. includes comprehensive evaluations by FDA, the National Institute on Drug Abuse (NIDA) and the Drug Enforcement Administration (DEA). Since 1970, the provisions of the CSA and international treaty obligations have provided a statutory basis for controlling access to scheduled drugs. Scheduling not only regulates and monitors the distribution of abusable drugs, it also serves to alert physicians to exercise additional caution when prescribing certain medications, particularly to patients who may be more at risk for misusing or abusing them.

3.4 For drugs with abuse potential, a formal risk management program (RMP) or a Risk Evaluation and Mitigation Strategy (REMS) may be required by FDA

Since the mid 1990s, FDA has increasingly relied upon RMPs to control access to drugs for which the provisions of the CSA were deemed insufficient to minimize abuse and diversion and REMS have been increasingly required since mid 2008 (Leiderman, 2009). It is important to understand that, even though conceptually CSA scheduling and the risk management program can be considered part of the overall risk management strategy, the regulatory mechanisms by which they are achieved are distinct. Final scheduling decisions, by law, are made by the Department of Justice/DEA, based in large part upon recommendations by FDA, and with potential input by NIDA (DEA, 2009). REMS, in contrast, can only be mandated by FDA. Using this mechanism, in most cases, FDA has required the RMP as a condition of marketing approval to further minimize abuse and diversion of scheduled substances (e.g., Xyrem®, Subutex® and Suboxone®), although in one case, Ultram®, a RMP was required as a substitute for CSA scheduling that was considered too restrictive (McCormick et al., 2009).

3.5 Risk management in various forms has the potential to make drugs with special concerns available to patients under conditions to limit their unintended consequences, including abuse

Successful RMPs allow patient access to drugs under conditions designed to limit abuse and diversion. RMPs may allow access to a drug that otherwise might not be approved by FDA.

3.6 The legal and regulatory status of risk management is in transition, with an unclear scope of authority for FDA to require risk management as a condition for approval of CNS active drugs

Nevertheless, risk management programs are increasingly being required to address concerns of the agency (e.g., for buprenorphine, sodium oxybate and the methylphenidate transdermal patch). In March, 2005, FDA issued three guidance documents for industry related to risk management, which are reviewed by Leiderman (2009). REMS are enforceable by FDA by virtue of Title IX of the Food, Drug, and Cosmetic Act Amendments of 2007, and until and unless FDA develops formal guidance documents for REMS, their development will be guided by the 2005 industry guidance documents and statutory provisions and descriptions contained in the 2007 legislation.

3.7 Risk management is an iterative process

As stated by FDA the iterative process includes: (1) assessing a product's benefit-risk balance; (2) developing and implementing tools to minimize its risks while preserving its benefits; (3) evaluating tool effectiveness and reassessing the benefit-risk balance; and (4) intervening and making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance. This four-part process should be continuous throughout a product's lifecycle, with the results of risk assessment informing the sponsor's decisions regarding risk minimization. What these statements imply is that when a signal that diversion and abuse are occurring is detected, the finding should lead to further investigation, evaluation and the development of an appropriate response (see Dart, 2009; Dasgupta and Schnoll, 2009).

3.8 Ideally, risk management should be based on a science foundation, as was certainly the intent of FDA, but it must be recognized that this is an emerging area of science

It was recognized that the science base for risk management is uneven with, for example, a strong foundation for predicting abuse liability and a weaker foundation for predicting which elements and tools of a risk management plan actually may reduce drug abuse and diversion.

3.9 While these guidance documents apply to the wide diversity of adverse events produced by all pharmaceuticals, their application to managing the adverse events of abuse and diversion requires unique strategies

The detection of signals of diversion and abuse, particularly by inappropriate routes of administration, is complicated for two primary reasons: 1) the risks are not confined to prescribed patients but apply also to non-patient populations that illegally obtain the drug; and 2) those who are unlawfully diverting and/or abusing the drug most likely will try to hide the activity. Adverse events of this nature are unlike adverse events related to other types of medications, which patients are fully motivated to report to their attending physician or health care worker under no threat of sanction.

3.10 Traditional surveillance surveys do not provide the timely, sensitive and accurate information required to guide the iterative process involved in risk management

An essential feature for effective RMP's is a post marketing surveillance approach that can detect the emergence of an abuse problem on a regional basis before the abuse of the medication becomes a major public health problem. Early detection, as in the case of infectious disease, is key to successful remediation. But federal surveys of abuse (e.g., National Household Survey on Drug Use and Health, Drug Abuse Warning Network, Monitoring the Future, etc.) are not designed to identify emerging problems, particularly problems involving specific marketed drugs. Moreover, findings from these national surveys are released two or more years after the collection of data. Currently, there are several groups that have developed methods to track emerging abuse problems with newly marketed medications. Their methods are designed to detect regional signals of diversion and abuse and may be useful for assessing the effectiveness of risk management interventions designed to address specific problems. However, the methods currently in use are not identical in their approach and the reliability and validity of these various approaches have yet to be determined. Moreover, it remains uncertain how these non-federal assessments will be funded over the long term. Lack of evidence-based tools is a major limitation in industry-run risk management plans and needs to be acknowledged and addressed, especially by FDA.

3.11 One of the factors driving the development of risk management strategies for CNS drugs in the U.S. is that the abuse of prescription opioids and stimulants has increased considerably in the last decade

Unfortunately, prescription medication abuse is a public health problem that transcends specific medical products making it difficult for any one company to develop a plan that will reduce the prevalence of the wider problem at the population level. Furthermore, surveillance needs to account for the fact that, compared to innovator drugs, generic drugs are abused to a far greater extent, mainly because they are cheaper, more available, and generally not banned by restrictive formularies. Also, their control appears to be outside of the risk management loop. Related to this issue is that even if RMPs were applied to all medications in a certain class of drugs, abuse and diversion of these drugs would probably not be entirely eliminated. The abuse of certain classes of drugs (e.g., opioid analgesics, sedative-hypnotics) appears inevitable and it is unrealistic to expect RMPs to completely eliminate it. Instead, the goal of RMPs is to minimize these risks to the lowest achievable level so that the benefits of a medication outweigh its risks. What is considered an acceptable level of abuse, however, or even if there should be such a notion as an "acceptable level" of abuse, is open to debate.

4. Recommendations

4.1 Laboratory-based studies for assessing the abuse liability of drugs that target new molecular sites, prodrugs, and novel dosage formulations need to be refined

Preclinical and especially clinical laboratory studies can provide evidence of the likelihood that a new drug will be abused. This information is essential for the development of RMPs, as noted in the conclusions. However, laboratory methods that assess abuse liability need to be improved and standardized for drugs that target new molecular sites, are prodrugs or use novel, tamper-resistant delivery systems and/or abuse-resistant formulations (Sellers and Johanson, 2006). Improved analytic strategies would also help to improve the interpretation of data for drugs producing weak or mixed signals in laboratory studies. This in turn would inform regulators as to whether scheduling is needed or appropriate as a component of a risk management plan. Laboratory-based interaction studies with alcohol and/or other drugs of abuse could also provide important information to guide the development of risk management strategies. Such studies are most important when there is evidence that meaningful interactive toxicity with alcohol or other drugs is likely, based upon what is known about the different entities' pharmacology. That is, the rationale for requiring such studies should be well justified. Laboratory-based methods also need to be developed to evaluate the attractiveness and appeal of innovator drugs or formulations with the challenge of developing appropriate scales for such subjective assessments. The tools of behavioral economics may be useful in this regard.

4.2 New types of data sources need to be developed to detect emerging problems and complete findings need to be released in a timely fashion

New sources for signals of abuse and diversion are needed and could include data from law enforcement, patients entering drug abuse treatment programs, prescribing physicians, poison centers, medical emergency departments, state prescription monitoring programs, key informants, media, government and third-party payers, and perhaps new types of federal surveys if they can be developed (Dart, 2009; Henningfield and Schuster, 2009). Sources need to be specific to geography, population, and product and include methods for assuring quality control. Because these sources will yield data that are both qualitative and quantitative, combining and interpreting such indicators will be challenging. Although sophisticated statistical methods can be used, signal detection will always remain highly dependent on clinical experience and human judgment (Dasgupta and Schnoll, 2009).

4.3 Post marketing surveillance techniques that detect a signal of diversion and/or abuse of a drug need to be followed up with both quantitative and qualitative field studies to assess the nature and magnitude of the problem suggested by the signal

Such information is essential for the design of tailored risk management interventions. Medications primarily abused by adolescents, for example may necessitate a different intervention than medications primarily abused by older adults. There is also a need to more effectively investigate the desired and undesired effects of risk management interventions, including establishing criteria for terminating a risk management and surveillance program. In the analyses, the magnitude of the signal must be considered in relationship to the total population that could become a case. The choice of a denominator is extremely important but highly controversial. More research is needed to evaluate the appropriateness of various types of denominators for specific drugs.

4.4 If it is determined that a signal is valid, the information can be used to develop an intervention including modification of the risk management program

As with signal detection, however, the effectiveness of interventions also needs to be evaluated. The same surveillance systems in place to detect a signal may also be useful for evaluating the effectiveness of follow up risk management interventions.

4.5 Evaluations of the effectiveness of RMPS as well as unintended consequences are needed

The gold standard of evidence-based practice is controlled observation in Randomized Controlled Trials (RCT). This gold standard might be applicable to the evaluation of the effectiveness of RMPs as well. However, RCT may not always be practical or appropriate so alternative designs must be considered. These include quasi-experiments, open-label trials, econometric modeling, and systems analyses approaches. Evaluations should include assessments of negative consequences, which could include unreasonably restricted availability to legitimate patients, onerous burdens on physicians or pharmacists, cost, or increased therapeutic use of less effective or more harmful drugs. At a later date, when the field has more experience, it might be useful to suggest that the Institute of Medicine launch a study to evaluate the success of the REMS legislation and FDA regulations designed to minimize the diversion and abuse of medications with abuse potential. Based upon the findings of research and interpretations by this body of experts, a revision of the guidelines and practices of FDA may need to be considered.

4.6 Because research on the efficacy of RMPs is in its infancy, it will be important to encourage the funding of research studies, including controlled trials when possible, to provide an evidence base for risk management tool efficacy and real world effectiveness

Ideally, much of this research would be done with governmental support instead of by the pharmaceutical industry to disentangle the separate interests of good study design and regulatory compliance. In the U.S., the National Institutes of Health and the Agency for Health Care Research and Quality are potential sponsors of research in this area and they should be encouraged to develop targeted programs. Another potential source for research funding might be consortia of pharmaceutical companies or umbrella organizations that represent them. This is not to say that individual sponsors should not undertake the very best program evaluation that they can when implementing RMPs for their own products, but to expect the support of controlled trials by individual sponsors may be a difficult goal to achieve.

4.7 The REMs legislation and regulatory strategies should ensure that within a class of drugs, generic and innovator drugs are held to the same standards for post marketing surveillance and risk management strategies including REMS

Sponsors of generic formulations of branded products whose sponsors are supporting RMPs should be expected to provide the same program as the branded product sponsor. In addition, raising barriers to marketing, prescribing, and patient access, and/or concerns about a particular drug by virtue of warnings and other risk management tools can result in patients being prescribed drugs for which there appears to be fewer concerns and barriers, even when those drugs carry the same or greater risk as the drug that is marketed with a risk management program. This unintended consequence must be taken into consideration in risk management program development to reduce unnecessary drug shifting, which may not reduce abuse and could deprive patients of more effective and appropriate medications. That is, the requirement for these risk management programs should not be imposed arbitrarily but consistently across products in the same class, which are likely to pose the same relative degree of risk.

4.8 Collaboration across federal agencies and health care providers to assure the management of risks related to abuse and diversion of pharmaceutical products are essential

For instance, to the extent that the RMP of a specific product by its developer identifies multi-product drug abuse problems, these are most appropriately referred to state and federal public health authorities with the primary jurisdiction over these issues. Related to this wider sphere of responsibility, greater clarity is needed about the responsibilities of state and federal agencies, medical societies and other stakeholders in addition to the sponsors of the multiple products being abused. Collaborative efforts between all of these groups should be encouraged on a regional or national basis depending on the nature of the signal obtained. In this regard, professional societies such as CPDD as well as FDA may have a role to play in orchestrating collaborative efforts and funding agencies should also be included in discussions of the development of science-based strategies. As acknowledged in the conclusions and other recommendations contained herein, the science of risk management and surveillance is in its infancy and only with a coordinated effort can progress be made. While the importance of RMPs for abusable drugs is obvious, requiring them prior to the establishment of a science base for the tools that will be used to design and implement them is problematic.

4.9 CPDD should convene a meeting of appropriate stakeholders to consider an examination of both the curriculum and the educational methods for training all health care practitioners in the appropriate prescribing of medicines with abuse potential

A continuum of professional training is needed to improve: the recognition and management of substance use disorders; the management of patients who require controlled substances or other medicines with abuse potential for legitimate medical purposes; the management of patients with co-occurring substance use disorders and conditions that would typically require the therapeutic use of medicines with abuse potential; the management of an aging population; the management of multiple co-occurring disease states, including substance use disorders and mental illnesses; and the delivery of health services, including substance use disorder and mental health services, as part of an integrated health care team.

4.10 New strategies for risk management of prescription drug abuse will require health care providers, caregivers and patients, to understand the requirements in order for them to be practically achievable, and for there to be incentives to comply with the strategies

The failure of prescribers and caregivers to adequately balance risk and benefit can undermine the best efforts at harm minimization. Physicians and other health care professionals are going to need expanded training in the identification of problems of drug abuse among their patients and in making medication selections based on these assessments. They are also going to need training in the reporting of problem behaviors and in appreciating their important roles in adhering to RMPs. Improved training of health professionals in problems of prescription drug abuse should begin with their initial professional training programs, as discussed above, but will also need to include improved access to continuing education and source materials about risk management. Another place for ensuring knowledge of drug abuse issues is in the licensing steps for health professions. For example, in the U.S. it may be useful to look at the requirements for obtaining a DEA registration as a potential place to ensure adequate knowledge. Some state medical boards require CME training in pain management as a condition for renewing one's medical license. Since prescription opioids are used in pain management and also are the category of prescription drugs most abused, including even a modicum of additional risk management training in these required CME courses could make a sizable difference in abuse rates.

Patients, too, will require better education, options and incentives to contribute to the prevention of medication abuse and diversion. For example, instructing patients to carefully

store a medication that must be taken daily and then to “properly dispose” of unused medications, may have little impact on actual patient behavior if the guidance is not clear and if there is not a practical means for complying with the guidance. Although patient education is part of many RMPs, more general knowledge among citizens about problems of drug abuse and their role as both enablers and perpetrators will be important to develop. Because teenagers and young adults comprise the largest cohorts of prescription drug abusers, patients with teenagers or young adults in their households should be informed of this special risk. Most abusers of prescription drugs report obtaining their drugs from relatives or friends who are prescribed the drug (SAMHSA, 2007).

4.11 Development of risk management programs, including REMS, should consider the potential impact on the drug pipeline and not just on drugs that are approved or pending approval

RMPS and REMS have the potential to either foster or stifle innovations in drug development. If all drugs with the same active pharmaceutical entity are required to have identical RMPs despite differences in dosage formulation that might affect real world risk of and consequences of abuse, there may be no incentive for drug developers to develop drugs that are more resistant to abuse.

Conflicts of Interest

Chris-Ellyn Johanson and Charles R. Schuster both participated in the planning of the conference. Dr. Schuster served as co-chair for the meeting as a whole and for the Expert Panel. As one of the authors of the introduction and commentary, he received compensation from CPDD. Dr. Johanson served as rapporteur for the Expert Panel and for her contributions to the Expert Panel and as well serving as one of the editors of the supplemental issue, she received compensation from CPDD. Dr. Schuster and Dr. Johanson are members of CRS Associates, LLC. CRS Associates has active consulting arrangements with Takeda Pharmaceutical Co., Shire Specialty Pharmaceuticals, Schering-Plough Corporation, Organon, Orexo, Apreva, Merck and Co, AstraZeneca, CoLucid, Consumer Healthcare Products Association, and the Institute for Behavior and Health, Inc. They also have a contract with Reckitt Benckiser Pharmaceutical Co for the postmarketing surveillance of Suboxone and Subutex.

Robert Balster participated in the planning of the conference that was the basis for this publication, serving as Co-Chair of the Planning Committee. As Guest Editor for this issue of the journal he received compensation from CPDD. He is Director of the Institute for Drug and Alcohol Studies and a Professor of Pharmacology and Toxicology at Virginia Commonwealth University. Both of these units receive pharmaceutical company contracts for pre-clinical abuse liability assessment research. The Institute is also the recipient of support from Reckitt-Benckiser for graduate student scholarships. He also serves as a paid consultant on abuse liability assessment research and regulatory matters to pharmaceutical companies, contract research organizations and trade organizations; recent and ongoing affiliations are with Abbott Laboratories, Alcologix, Alpharma, Astra Zeneca, Eisai, Johnson and Johnson, Global Biodevelopment, Pfizer, Servier, Shionogi, TAP Pharmaceuticals and the Consumer Healthcare Products Association. He also receives an honorarium and some royalties from Elsevier for serving as Editor-in-Chief of *Drug and Alcohol Dependence*.

Jack Henningfield is an employee of Pinney Associates, which has contracts with several pharmaceutical companies regarding regulatory issues. These include GlaxoSmithKline, Pricara Ortho-McNeil-Janssen Pharmaceuticals, Purdue Pharma and Shire Specialty Pharmaceuticals in which work has involved support of risk management.

James Anthony has no conflicts to report.

Andrea Barthwell is a member of Encounter Medical Group, PC., which has an active consulting agreement with GW Pharmaceuticals.

John J. Coleman, PhD, is president of Prescription Drug Research Center LLC (PDRC), a subsidiary of Bensinger, DuPont and Associates (BDA). PDRC and BDA have consulting agreements with Johnson & Johnson, Novartis, Abbott, and CoLucid. Robert L. DuPont, M.D. is president of the Institute for Behavior and Health, Inc. (IBH), and a partner in BDA. PDRC consults for and works closely with IBH. PDRC's major business line is providing risk assessments and risk management programs for pharmaceutical clients.

Richard C. Dart is Director of Rocky Mountain Poison & Drug Center (RMPDC), a department of Denver Health and Hospital Authority, a public hospital that operates the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System. RMPDC receives research and consulting contracts from various pharmaceutical companies involved in risk management of prescription medications (Johnson & Johnson, Purdue Pharma, Reckitt-Benckiser, Abbott Laboratories, Cephalon, Labopharm, Cumberland Pharmaceutical, Endo, and others). Dr. Dart receives no compensation directly from any company, including employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications, registrations, or grants.

Charles Gorodetzky has active consultant contracts with US WorldMeds, LLC and Catalyst Pharmaceutical Partners, Inc.

Charles O'Keeffe is on the Board of Directors of Catalyst Pharmaceutical Partners, Inc., Human Resources Inc., and is a principal in Kingston Pharmaceuticals LLC. He also has a consulting arrangement with Reckitt Benckiser Pharmaceuticals Inc.

Ed Sellers is an employee of Kendle International. Kendle is a global full service CRO that provides services to the biopharmaceutical industry, including the conduct of human abuse liability studies and drug abuse related regulatory and drug development consultation.

Frank Vocci is presently the president of the Friends Research Institute and has consulting arrangements with Catalyst Pharmaceutical Partners, inc., Glaxo-Smith-Kline, Reckitt Benckiser, Synosia, and US World Meds.

Sharon Walsh is Director of the Center on Drug and Alcohol Research and a Professor of Behavioral Science and Psychiatry at the University of Kentucky. She has received research support from World Meds, Inc. and Catalyst Pharmaceuticals. She has served as a paid consultant on abuse liability assessment research and medications development to pharmaceutical companies, including Abbott Laboratories, Meda Pharmaceuticals, and Yaupon Pharmaceuticals. She has also received honoraria and travel support as an invited speaker for Reckitt-Benckiser.

Acknowledgments

Role of Funding Source

Funding for writing the expert panel reported was provided by the College on Problems of Drug Dependence.

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