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# Abuse liability assessment of CNS drugs: conclusions, recommendations, and research priorities

The Expert Panel

## 1. Description of the process used to develop the conclusions, recommendations, and research priorities

The College on Problems of Drug Dependence meeting on the abuse liability assessment (ALA) of CNS drugs was intended to provide a forum for discussion of the present state of the science of ALA (Schuster and Henningfield, 2003). The meeting was attended primarily by representatives from four groups interested in ALA of CNS drugs: (1) experts from academic medical and research institutions who are actively engaged in developing procedures for ALA and performing such assessments; (2) United States governmental agencies that regulate and develop policy for drugs with a liability for abuse; (3) pharmaceutical companies that develop and market CNS drugs; and (4) professional and nongovernmental organizations with a major interest in the methods and clinical implications of ALA. The participants were limited to approximately 80 in order to facilitate discussion. In addition, the conference was available by web cast offsite, so that others could view the proceedings in real time over the internet.

The purpose of the meeting was to provide an update on ALA of CNS active medications. ALA is not a simple test but rather it is a scientifically guided strategy for developing an objective basis for the regulation of drugs. Appropriate drug regulation is intended to ensure that the medical needs of patients can be addressed without undue or inappropriate limitations to access while also preventing abuse through the provisions of the Controlled Substances Act (CSA) (see Spillane and McAllister, 2003, this volume). This requires predicting the benefit to risk ratio of medical to nonmedical use<sup>1</sup>. A key assumption in this process is that abuse liability varies along a continuum and the level of control for a specific drug should be appropriate to its medical benefit and the risk of abuse. ALA provides the science base for

establishing controls that achieve a balance between access and prevention of addiction.

The College on Problems of Drug Dependence (CPDD) has had a long interest in this topic, and it has been the primary professional organization devoted to research in the area of abuse liability. The College has served as an effective intermediary between governmental agencies and the pharmaceutical industry in the past, and attempts to function as an agent that interacts with all interested parties in an unbiased manner. A similar conference sponsored by CPDD, and attended by similar representatives as the current meeting, was held in November of 1988 in Princeton, New Jersey, and proceedings of that meeting were published as a National Institute on Drug Abuse (NIDA) monograph (Fischman and Mello, 1989). The College felt that there were three compelling reasons to organize the current meeting. First, new and novel medications that do not fit into traditional categories of abused substances are being developed. While testing procedures for some classes of medications are relatively well established (e.g. opioids and sedatives), similar consensus for evaluation of such novel medications has not been explicitly achieved by the various interested parties. Second, there has been considerable evolution in the thinking about clinical populations that might be studied as part of an ALA since the 1988 meeting. For example, persons with the target disorder, or those at high risk for abuse after approval and marketing of a new medication, are relatively new groups that could be studied as part of a broader and more comprehensive assessment of abuse. Finally, the role of various, and at times new, research methods and tools in the assessment of abuse liability needs to be clarified. Under the somewhat unique circumstances of ALA—where considerable work is done at academic centers rather than directly by the pharmaceutical company developing the compound—agreement on tools and appropriate practices that are used across centers would be valuable. It was realized by the planning committee that each of these motivations for the conference could result in extensive presenta-

<sup>1</sup> Other factors, such as safety and side effects, can also influence a final determination of a medication's value.

tions, deep and lengthy discussions, and considerable debate, but the overall goal of the meeting was to initiate a dialog among interested parties and identify areas requiring further effort and development. The meeting was not meant to answer all questions, but rather to recognize topics that require further discussion and research and alert the interested parties that further research in this area is needed.

Before the meeting was held, a series of pertinent topics were identified by the organizing committee. Members from CPDD were commissioned to write review papers on each of these topics, which were completed prior to the meeting (and are available after revision, in this special issue). The authors of these papers were instructed to prepare a relatively brief presentation for the conference based upon their manuscript.

The organizing committee also identified an expert panel prior to the meeting. This panel was to listen to the presentations and discussion, actively interact with the attendees at the meeting, seek out and question participants and presenters, and then utilize the formal presentations, papers, and discussions to develop the foundation for a set of conclusions, recommendations, and identification of research priorities. The panel, under the leadership of Dr. Edward Sellers, is responsible for this report, and its members are listed in Table 1.

The specific charge to the expert panel by the conference conveners was to develop conclusions and recommendations on the state of the science of ALA, in order to provide a framework for ALA that would serve drug developers, drug regulators, and research centers. An additional charge was to identify research needs to serve investigators, research organizations, and funding

institutions. When developing this framework, the expert panel was reminded of the importance of fostering appropriate use and access to medications by patients in need, while providing appropriate levels of control over CNS active drugs with the liability for abuse.

The conclusions and recommendations were developed according to a protocol developed prior to the meeting. The first step was to determine the focus of the meeting and priority areas for consideration as discussed above. This formed the basis for the commissioned papers that were developed for the conference and presented during the first day of the conference. At the end of the first day, the panel met to identify specific topics for discussion and consideration by the meeting participants during the morning of the second day. The post paper and second day discussions formed the basis for the development of draft conclusions and recommendations, which were then presented during an afternoon session on the second day. This provided an opportunity for additional input from the meeting participants. Additional comments were provided following the meeting and modifications were made to improve clarity. The conclusions and recommendations are not implied to constitute a consensus of all conference participants; however, the intent of the panel was that its product would be a credible representation of the workshop and that it would provide a framework to serve regulatory agencies, drug developers, research institutions, and public health.

## 2. Conclusions

(1) *ALA has served to protect public health in the United States and globally by producing information useful to drug regulatory agencies in their control of CNS drugs.* Assessment of abuse liability has been a valuable process that is typically sponsored by either the pharmaceutical industry or the government (primarily the National Institute on Drug Abuse, NIDA), conducted primarily by members of the academic research community, and utilized primarily by governmental agencies such as the Food and Drug Administration (FDA) and the Drug Enforcement Administration (DEA). While each of these three parties has particular interests and goals, together the three have historically provided an effective mechanism for funding ALAs, conducting controlled studies and generating data regarding abuse liability, and making regulatory decisions that are scientifically based. The overall system is a good one that should be acknowledged as having been highly successful.

(2) *There is a broad range of drugs that potentially warrant ALA.* Many medications for treating medical conditions may require ALA, especially if such medica-

Table 1

Members of the expert panel of the College on Problems of Drug Dependence meeting on the Abuse Liability Assessment of CNS drugs

### Chair

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### Members

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tions have CNS effects. Testing for abuse liability is not necessary for all CNS medications that are developed, but the consideration of why testing is required or not required should be a part of the development process, regardless of indication or drug class. For new medications with actions that are similar to known, non-abused medications, this consideration may be relatively straightforward. However, for medications with novel mechanisms of action or indications, a careful, thorough, and documented rationale for why an ALA is warranted or not warranted should be made.

(3) *An ALA provides a framework for determining whether or not a drug should be placed under the CSA and, if so, the level of control.* The rationale for the decision regarding scheduling should be clear to all parties, and should be based upon all available research and data (e.g. post-marketing data in another country). All results from an ALA should be utilized when making decisions regarding scheduling. If there is insufficient information for making a decision, then further assessment should be conducted rather than erring on the side of more restrictive scheduling.

(4) *In the process of developing a new medication, preclinical data regarding abuse liability are critical for early decision making.* Animal models and procedures for assessing abuse liability are well established, and results from preclinical assessments can provide compelling justification for the need to conduct further clinical testing. While there are exceptions where abuse in humans is not mirrored in animal models, and vice versa, there is a broad set of drug classes that show common features of abuse in preclinical and clinical testing.

(5) *Confidence in predictions is increased when data are considered across a range of control conditions and drug doses. The overall profile of the drug is critical to understanding its liability for abuse.* When assessing for abuse liability—either in the preclinical laboratory or in human subjects—optimal detection of abuse liability requires the use of appropriately selected control conditions, a broad array of assessments, and multiple doses of the new medication being studied (Ator and Griffiths, 2003, this volume; Griffiths et al., 2003, this volume). A final decision of abuse liability should be based upon all of these factors (ability of controls to detect the expected abuse profile effect; detection of abuse on multiple measures; an adequate range of doses of the new medication tested). Conference participants agreed that data from any single outcome measure (e.g. single scale on a subjective effects questionnaire) was insufficient and could not be used alone to conclude that a medication will or will not be abused. Decisions, instead, should be based upon a broad spectrum of evaluations from both preclinical and clinical studies.

(6) *Currently, pharmacologic profiles are relatively well characterized for opioids, stimulants and sedative-hypno-*

*tics. These profiles provide a general framework for evaluation of new compounds.* When evaluating new compounds, prototypic drugs from the most relevant pharmacological class should be tested as a positive control along with the new compound. If a study fails to detect meaningful abuse liability for the control drug, then the overall study results must be considered suspect, although the results are not necessarily invalid. If the compound being studied has a novel mechanism of action, then multiple control comparisons should be included in the ALA.

(7) *Models for the assessment of abuse liability in humans have been established and these models have been useful for assessing the risk of abuse of new drugs and drug formulations.* The primary clinical model used for testing abuse liability has been the laboratory-based study, typically conducted on an inpatient basis and utilizing a within-subject design. Human laboratory studies have assessed the relative abuse liability of different opioids, stimulants, and sedative-hypnotic medications and have generally yielded valid results and thus may be useful in predicting the abuse of a medication when it used in clinical practice. If a clinical assessment for abuse liability of a medication is planned, then consideration should be given to an assessment based upon some form of the methods that have been developed for human laboratory evaluations of abuse liability, although it is recognized that further development of these procedures is warranted to increase sensitivity and selectivity.

(8) *Drug abusers are an appropriate population in which to study abuse liability.* Studies with drug abusers can be ethically conducted as long as procedures are in place for adequate human subjects review and monitoring. In fact, the drug abusing population has historically been the population of choice in assessments for abuse liability. The choice of this population is based upon prior demonstrations that evaluations utilizing drug abusers and that are conducted in the laboratory yield results that predict abuse. The literature with other populations is not as extensive and further research to determine the appropriateness of other populations is needed.

(9) *Failure to detect a signal of abuse liability in a drug abusing population is good evidence of lack of abuse liability in less vulnerable populations. However, a positive signal in this population is not sufficient to conclude that there is risk of abuse to a wider population.* For example, it may be the case that there is an increased risk of abuse of a new medication in a particular sample of drug abusers, but there is a relatively low risk of abuse in the general population. Detection of a positive signal in drug abusers—evidence that there could be abuse of the new medication—should result in further assessment during the drug development process (such as closer monitoring of diversion and abuse during large out-

patient clinical trials testing efficacy and safety or ALA in other populations).

(10) *Testing a range of doses is important, especially with novel compounds, although the use of high doses can raise safety and ethical questions. Therefore, ALA should include the widest range of doses that can safely and ethically be administered.* Specifically, where feasible, doses should include those greater than the expected maximum therapeutic dose, because experimentation by certain populations with higher doses of a medication may occur. Procedures such as testing initial volunteers according to an ascending dose sequence may be necessary as a first step in the ALA to ensure that a wide range of doses can be administered safely. Limiting testing to only low or therapeutic doses of a medication may produce results suggesting no abuse liability for a medication that subsequently is abused at higher doses.

### 3. Recommendations of specific strategies

There are a wide range of CNS drugs in various stages of development that would be subject to review for potential scheduling. These include new formulations of already scheduled drugs, chemical entities with similar structure or function as already scheduled drugs, drugs for indications in which abuse is of particular concern (e.g. a medication being developed to treat cocaine dependence), and novel CNS agents unlike any drug of abuse. These need to be assessed for abuse liability to enable their sponsors to determine whether and how development should continue. For instance, abuse liability of a formulation of an already marketed analgesic will influence decisions regarding scheduling, labeling, restrictions on marketing, and target patient populations. Further, if a sponsor is developing a new drug that does not have increased efficacy versus established medications, but hopes to substantially increase access to the medication by obtaining less restrictive scheduling because it might be less abused, then it is critical to assess the abuse liability as accurately and as early as possible in the drug development process. To accomplish this, it is important that pharmaceutical developers should test their drugs using strategies that are likely to be considered definitive by the agencies that contribute to drug scheduling decisions (namely, FDA, NIDA, and DEA).

The expert panel understands that the recommendations of specific strategies listed below are not binding on federal agencies but submits these recommendations as a peer vetted basis for evaluating the level of confidence in the validity, reliability, and generality of various procedures, as well as what steps need to be taken to further the rational assessment of abuse liability. This is important because an explicit recognition and acknowledgement of the scientific strength of

ALA is necessary in order to efficiently and expeditiously develop important new drugs. The drug development process could be substantially retarded by uncertainties about testing methods and/or the perception that scheduling decisions will be strongly based on considerations other than the objective ALA. The following recommendations are intended to serve this purpose by providing a framework for ALA.

(1) *A decision-making algorithm should be developed for staging the steps of ALAs to improve decision making and communications over the course of drug development.* Pharmaceutical development includes constant decision making at each stage of progress to guide next steps. It appears useful to pharmaceutical developers, researchers, and regulators alike to understand the core elements of a decision making algorithm even assuming that all parties do not fully endorse it and assuming that any algorithm will necessarily be applied with some flexibility. A useful example of such an algorithm was discussed at the meeting and it is presented in this volume (Mansbach et al., 2003, this volume).

(2) *CPDD should facilitate research in the development and application of ALA.* Following are several of the specific ways that were discussed.

- 1) Facilitate research in ALA by using CPDD's web site to post archival documents relevant to research and regulation.
- 2) Identify core methods, outcome measurements, and statistical analysis plans for animal and human ALA.
- 3) Work with researchers, regulators, and pharmaceutical developers to identify such core components while recognizing that flexibility is needed to accommodate new drugs, drug formulations, and improvements in scientific methods.
- 4) Conduct educational programs to facilitate application of Good Clinical Practice (GCP) standards and other regulatory considerations for clinical studies that are part of the ALA (see Section 3(3)). This suggestion should not be interpreted as a recommendation that CPDD become involved in accreditation.
- 5) Facilitate the development of partnerships that include representatives of research organizations, regulatory agencies, medical societies, and consumer/patient advocates, and use the regular meetings of CPDD as a setting for continued communication of new approaches and issues related to abuse liability research.

(3) *Clinical research laboratories that conduct ALA should be encouraged to move toward complete adherence to GCP standards.* Research and testing intended to support new drug applications must meet GCP standards and the conference participants agreed that with

the possible exception of research on methods development, drug evaluations should be conducted according to GCP standards. It was recognized that this may result in some academic laboratories focusing exclusively on research and not incorporating the additional procedures necessary for drug evaluations intended to support new drug applications, largely because of cost issues. On the other hand, it was not considered appropriate for preclinical studies that are part of the ALA to adopt the stringent technical regulations of Good Laboratory Practice.

(4) *Clinical trials have potential as a source of early signals relevant to ALA as well as to the risk and significance of abuse and withdrawal manifestations in clinical populations, but little research has been done in this regard.* When designing clinical trials, especially large, between group comparison studies for a new medication, consideration should be given to having abuse measures incorporated into such studies. If a clinical trial plans to use results to inform the abuse liability of a medication, then there should be a proactive plan for assessment of abuse with specific measures that are collected at multiple time points over the course of each participant's time in the study. The range and type of such measures used in clinical trials could be based upon results from earlier ALAs, such as human laboratory studies with drug abusers, e.g., subjective effects batteries. Assessments could also include adverse event reports, measures of diversion and non-prescribed patterns to use of the medication.

(5) *Once a drug is marketed assessing abuse liability should continue. Post-marketing surveillance systems should be viewed as one component of a comprehensive package of assessments that includes preclinical assessments, human laboratory studies, and outpatient clinical trials.* However, the science of post-marketing surveillance systems is still in its infancy. National surveillance systems are potentially a source of signals relevant to ALA, but are limited in their ability to provide a sensitive and valid early warning system for detecting abuse of a medication. These systems—such as the National Household Survey of Drug Abuse—are sensitive to detect recent changes in abuse rates and patterns of use of drugs that have been available for some periods of time. They should not be considered as a sufficient assessment of the abuse liability for a newly marketed medication. The abuse of a new drug progresses slowly and does not become nationally visible until sufficient time has passed for the development of an illicit market. While the rapidity with which information about a new drug of abuse spreads it has increased considerably with the advent of the internet, results from monitoring the internet (e.g., discussions in chat rooms) should be interpreted with extreme caution. Such information can be of interest, but should be primarily used to initiate well-designed post-marketing surveillance re-

search. A similar caveat applies to unsubstantiated case reports reported voluntarily to regulatory agencies.

(6) *An appropriate scientific framework for post-marketing surveillance studies should be developed.* It is especially important to determine the appropriate comparators against which to evaluate the incidence of abuse or misuse of a new drug. Post-marketing evaluation of abuse and misuse requires appropriate baseline data and context of use to evaluate the extent and nature of diversion and abuse problems. This, in turn, can be used to guide appropriate corrective actions which reduce such problems without unintentionally hindering patient access (see Arfken and Cicero, 2003, this volume). Analysis of misuse and abuse should be based upon all available comparison data, and response to such problems should take into account these comparisons. The level of concern and the nature of the response need to be proportionate and appropriate to the nature and relative level of the problems.

(7) *A glossary of terms used in ALA should be developed to improve communication among sponsors, academia, and governmental agencies.* It was recognized that a variety of terms have meanings that can vary across institutions and disciplines. For example, 'dependence' can be used differently by clinicians (as a clinical diagnosis) versus pharmacologists (as in physical dependence); similarly, any use of an illicit substance might be considered 'abuse' from a legal perspective whether or not it meets criteria for abuse from a clinical perspective. The development of agreement on the use of such terms is not intended to replace the nomenclature developed by clinical, regulatory, or other organizations, such as professional groups, but to facilitate communication by decreasing ambiguity.

(8) *Develop a guidance document for ALA with input from researchers, pharmaceutical developers, and federal agencies.* There is a history of periodically producing guidance documents on ALA that have served regulatory agencies, pharmaceutical developers and researchers (see Balster and Bigelow, 2003, this volume). Such documents are most valuable when there has been mutual development, contribution, and acceptance by all relevant stakeholders. Given the changes in the ALA field noted in the introduction of this paper (new and novel medications, new potential study populations, new research methods), it would be extremely useful for CPDD to take the lead in organizing the updating of guidelines.

(9) *It needs to be recognized that research should be the joint responsibility of research institutions and pharmaceutical developers, as well as regulatory agencies and third party payers for medical care, because all have a common interest in the improvement of public health through appropriate drug control, which serves to prevent drug abuse while not hindering appropriate clinical access.* The long-term benefits of ALAs are incurred by a wide

range of parties (e.g., decreased liability by drug manufacturers; lower harm to society through less diversion and abuse). Research and development of methods for ALA across a variety of settings (e.g., preclinical studies, clinical trials, post-marketing surveillance) have grown substantially in complexity and cost. Adequate development of new methods and application of ALA procedures increasingly requires mutual contribution and support by the various stakeholders. All groups that benefit from ALAs need to contribute to the support of these procedures.

#### 4. Research priorities

It was apparent from the discussions that ALA continues to be an important focus of activity for researchers and should be an important focus of funding by research institutions. The methods of ALA continue to provide important tools for investigating drug action and exploring the mechanisms of behavioral and physiological effects related to abuse, dependence and withdrawal. However, it is evident that the continuing evolution of methods utilized in abuse liability research is important in order to continue to improve the reliability, validity, and generality of these methods.

Evolution in methodology will undoubtedly be critical to more effectively address the challenges posed by drugs with novel mechanisms of action and new formulations. Advances in medication development may yield new therapeutics with decreased abuse liability compared to existing and approved drugs—but no significant difference in efficacy outcomes. Such lower abuse liability may warrant differences in labeling and marketing restrictions even though the drug may be in the same class as a known drug of abuse. In such cases, new ALA methods with greater predictive power and sensitivity will be important components of the approval and scheduling processes.

An important caveat discussed at the conference is that the evolutionary process of methodological improvement is likely to be dynamic, but the need for such development should not imply that current procedures are invalid and not useful in decision making. The following recommendations are intended to generate research that will foster the continuing improvement of the methodology that will build on an already solid scientific base. The specific priorities are presented in italics and each is accompanied by a brief discussion to clarify its context.

(1) *Research should be undertaken on models for predicting abuse liability in the intended patient population in order to determine abuse risk and determinants of iatrogenic addiction.* Methods of abuse liability have historically emerged from pharmacological research which viewed abuse liability as a specific characteristic

of a drug. However, it is increasingly evident that the patient population itself is an important determinant of abuse liability risk. For example, there is generally less concern about abuse of dopaminergic agonists by patients being treated for depression than for patients using medications with dopaminergic activity to control body weight. Developing models of ALA that are specifically relevant to the intended patient population would, therefore, be valuable.

(2) *Research on the extension of ALA to new drug classes, populations, drug forms and indications should continue.* ALA procedures were systematically extended from opioids to sedatives, stimulants, and hallucinogens from the 1940s to the 1960s. However, the development of ALA methodologies to test new classes of drugs with novel mechanisms of action, differing time courses of effects, and qualitatively different effects has not matched in recent years the active efforts of pharmaceutical developers to develop drugs with novel profiles to more effectively and selectively treat various diseases. It would be expected that a major commercial incentive in novel drug development is to develop medications with lower abuse liability than competing drugs, and this will require validated and more sensitive models for assessing novel drugs.

(3) *Animal and human research are needed that provide better characterization of the diverse factors that can alter the risk of abuse and dependence. It has been increasingly recognized that the risk of abuse is not random across individuals but often is influenced by specific individual and environmental factors.* These factors can include genetically conferred differences in drug response or pharmacokinetics, as well as environmental factors such as stress, social modeling and availability of alternative reinforcers. Some progress has been made in these areas, but considerable research is needed to better understand a greater array of vulnerability factors for drug use, and how these vulnerabilities interact. Such information can serve to more carefully select study populations for ALA, and may inform post-approval plans (post-marketing surveillance strategies) for target populations that may be at particular risk for abusing a medication.

(4) *A database for new drug classes should be developed that provides a characterization of the profile of new drugs and a corresponding profile of effects for known drugs.* Developing and cataloging extensive behavioral and pharmacological profiles of drugs that are widely available are important aspects of developing and validating new assessment models. This proposed effort would enable comparison of new drugs along a variety of dimensions and may be critical in predicting the risk and conditions that would foster or mitigate abuse of the new compounds.

(5) *Scales should be developed to assess withdrawal and discontinuation symptoms in clinical studies.* Drug withdrawal symptoms or what may be referred to as

discontinuation symptoms occur when medications are abruptly or in some cases gradually discontinued. Such symptoms are important to quantitatively and qualitatively evaluate in clinical studies. However, there has been relatively little work to develop objective methods to obtain such data in this context (see Brady et al., 2003, this volume). This will be increasingly important as new medications are developed with the intention of minimizing such symptoms or which may have a propensity to produce such symptoms.

(6) *Methods to test abuse liability of different drug formulations should be developed.* Modifying drug formulation is an increasingly used method of developing products with more desirable clinical actions (e.g., slower onset, protracted effect) as well as to enhance safety and reduce abuse liability (e.g., by decreasing the ability to extract the active drug constituent for illicit use or by adding an antagonist). For example, nicotine, in the form of a polacrilex gum or transdermal patch, is relatively unattractive as a primary means of delivering nicotine for nonmedicinal purposes relative to cigarettes. In addition, a major area for development of controlled-release opioid analgesics and other substances (e.g., methylphenidate) involves an attempt to develop tamper resistant formulations because of the high doses contained in the formulation. However, abuse liability testing has traditionally been done with a primary focus on the chemical entity itself, and with relatively little consideration to the actual marketed formulation (as discussed by Balster and Bigelow (2003), this volume and Mansbach et al. (2003), this volume). Developing methods of ALA that take into consideration the planned formulation as well as factors such as the potential for tampering with the formulation to defeat its mechanism of slowing down rate of onset of drug effect and delivering a large drug dose over a protracted period of time are expected to be increasingly important to drug scheduling.

(7) *Researchers should be encouraged to standardize some psychometric scales (e.g., drug liking scales) for human ALA studies, in order to facilitate comparisons of ALA across research laboratories and across drugs.* Investigators frequently modify assessment instruments or develop new but unvalidated scales with the intention of improving methods of ALA (as discussed by Griffiths et al. (2003), this volume). This complicates cross study comparisons, and is especially problematic with evaluations of new drugs for which there is uncertainty as to the most appropriate comparator drugs and methods. It can lead to the use of many similar yet significantly different methods to evaluate a new drug, which, in turn, often results in mixed results that greatly complicate interpretation. This does not mean that research should not continue on the development of more refined psychometric scales but it does require that investigators validate new methods, which is not a simple task. It is

anticipated that it may be difficult to reach consensus on a standardized battery and even if developed, investigators may be reluctant to use such a set of assessments. At the least, a standardized battery could be one component of the evaluation, leaving investigators free to add other nonstandardized assessments.

(8) *Further studies on the incidence of 'iatrogenic addiction' and the factors that influence its development are needed.* It has been widely assumed that the risk of iatrogenic addiction for properly prescribed medications is very low. While there are little quantitative data to support a change in this conclusion, at least three facts make this an important priority for research: (1) iatrogenic addiction has been documented across several classes of drugs and therefore is known to be a real phenomenon; (2) there is a dearth of empirical research documenting the actual incidence and prevalence of iatrogenic addiction and the factors that modulate its risk; and (3) concern about iatrogenic addiction by some medical practitioners, patients, and drug regulators is substantial and possibly contributes to under use of medications, which in turn can lead to needless suffering by patients and as well could contribute to invoking more control than warranted.

(9) *Scientifically validated methods of post-marketing surveillance (including observational studies) need to be developed as a means for detecting early signs of abuse in the most vulnerable populations.* Post-marketing surveillance approaches are increasingly being used to address potential risks of abuse and misuse in diverse patient populations as well as populations that may be particularly vulnerable (e.g., a new opioid analgesic in pain patients or patients with a history of opioid abuse). These studies are now being initiated immediately following the introduction of a new drug because of the realization that national surveillance systems already in place are not adequate to detect a small signal. It is important to develop and evaluate new methods of surveillance to meet the challenges of a rapid assessment of abuse liability in small samples so that interventions (risk management strategies) can be introduced very quickly. The science of post-marketing surveillance is only beginning and the validation of methods will require diligence.

(10) *The impact of drug control mechanisms (e.g., the influence of scheduling) on clinical use and abuse of medications, as well on drug development and research, needs to be evaluated.* The CSA has served for approximately three decades as the primary guide for regulatory oversight and marketing conditions of drugs meeting criteria as controlled substances. Yet the impact of various provisions of scheduling is not clear. It is also not clear whether these provisions match changes in the practice of medicine, drug marketing, and the nature of the drugs. Increasingly, governmental agencies are applying 'risk management strategies' to reduce the

risk of drug abuse and diversion. Such strategies are developed on the basis of expert committee recommendations, but with relatively little empirical data. This is expected to be an increasingly important area of research, as such risk management interventions are increasingly applied, and as new drugs are developed with novel pharmacologic profiles.

## 5. Closing comments

As was evident at the conference and reflected in the papers presented in this volume, the science of ALA has been a fruitful area of research and a valuable component of drug development and evaluation. ALA has served pharmaceutical medications development by aiding in decision-making. In parallel, ALA has served the regulation of drugs through governmental agencies, and by providing an objective basis for determining appropriate scheduling, labeling and marketing restrictions. ALA thereby continues to contribute to public health by helping drug developers and drug regulators to achieve the goals of providing adequate access to medicines by patients while reducing the probability of abuse. Continued research should foster the necessary evolution of the science to meet the challenges that future medications development will bring.

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