Incorporating the assessment of abuse liability into the drug discovery and development process

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Abstract

Evaluation of abuse liability is one of many obligations incurred by industrial sponsors in the development of medications acting on substrates in the central nervous system. In addition to providing the information necessary for a scheduling recommendation in the marketing application, the abuse liability assessment allows sponsors to estimate safety and commercial risks associated with scheduling, as well as to tailor their pre- and post-approval programs to collect information relevant to product misuse, illicit diversion and physical dependence. There are several important factors to consider before embarking on an abuse liability assessment, including the compound’s primary and secondary biochemical activities, its absorption and metabolism, its final formulation, and its intended clinical population. Each of these factors will temper the timing and extent of the abuse liability program in animals and humans. Although every drug development program is unique in some way, a decision-making process may be applied to abuse liability assessment that will serve to better utilize limited resources and inform decisions regarding subsequent steps in the process. The emerging properties of the product will define the unique procedures best applied to assess it.

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1. Introduction

Recent years have witnessed an increasingly intense search for new medications to treat psychiatric, neurological and pain disorders. In their quest to develop compounds with increased efficacy, improved safety profiles and utility in treatment resistant populations, industrial sponsors have harnessed new technologies that yield molecules and drug products with unprecedented properties. Before being approved for use in the United States, however, all such investigational drugs must undergo a risk-benefit analysis as part of the New Drug Application (NDA) review. Among the factors that must be evaluated in the NDA is the medication’s risk for misuse, physical dependence and addiction (Code of Federal Regulations, Title 21, Part 314.50). If the drug is determined to have potential for abuse, its use may be restricted under the Controlled Substances Act (CSA). Accumulating research has shown that attitudes created by drug scheduling can negatively affect physicians’ prescribing behavior (e.g. Brown et al., 1997; Weinstein et al., 2000). Because scheduling is often perceived by physicians as an unfavorable attribute, particularly if there are nonscheduled drugs available to treat the same condition, abuse liability may be considered a point of differentiation that has profound implications to the product’s ultimate clinical and commercial success. Thus, sponsors have at least several reasons to evaluate new developmental compounds for abuse potential: (1) to provide information that assists in developing an accurate, evidence-based risk-benefit assessment; (2) to satisfy regulatory requirements and thus assist the Food and Drug Administration (FDA) and the Drug Enforcement Administration (DEA) in striking a balance between patient access and...
The majority of drugs scheduled under the CSA exert their primary therapeutic actions in the central nervous system (CNS), and it is widely acknowledged that drug reinforcement is mediated through CNS substrates. Table 1 presents examples of controlled substances and their therapeutic uses. There is a separate process for the scheduling of anabolic steroids; however, the basis for abuse of this drug class is different and will not be considered in this chapter.

In a sense, all drugs entering the CNS may initially be viewed as having a potential risk for abuse. Thus, the decision for sponsors is not so much whether to evaluate the drug for abuse liability, but how early to evaluate it and at what level of intensity. Extensive epidemiological, clinical and laboratory evidence has identified a number of drug classes that are abused, and these are clearly identified in the CSA. Moreover, neurobiological research has identified neurotransmitters and brain circuitry that appear to underlie the reinforcing effects of these drugs in animals and humans. With the availability of rapid screening assays at the cellular and molecular level, the interaction of compounds with known targets of abused drugs can be readily ascertained and the intensity of the evaluation escalated accordingly.

However, in many cases the nature of a new drug’s interaction with reinforcement pathways, if any, is not obvious from preliminary biochemical assays. Modern CNS drug discovery programs strive to discover and develop molecules with increasingly fine-tuned and subtle targets of action. The properties of such drugs vary along the dimensions of primary target, target selectivity, intrinsic efficacy, and pharmacokinetics. As such, ideas for a drug discovery program may fall into one of four scenarios, each of which confers a certain range of risk of abuse potential. These classes and their corresponding a priori risks are: (1) the proposed target and pharmacodynamic effect are the same as a compound known to have abuse potential (high risk of abuse potential similar to the known compound); (2) the proposed target and pharmacodynamic effect have similarities to and differences from a compound known to have abuse potential (intermediate risk of there being some level of abuse potential); (3) the proposed target and pharmacodynamic effect are the same as those of a compound known to have no abuse potential (little or no a priori risk of abuse potential); (4) the proposed target and pharmacodynamic effect are entirely novel (risk of abuse potential entirely unknown). The timing and extent of an abuse liability assessment for CNS drugs thus depends upon this assessment of risk. As with other aspects of drug safety, this assessment is repeatedly modified by the addition of new information during the drug discovery and development process. For example, a compound may be discovered to exert unintended secondary actions that are similar to those of drugs with known abuse liability.

Because the evaluation of compounds for abuse potential will often evolve as more is learned about the compound, it is of value to consider aspects of the drug, its biological target, its formulation and its target clinical population as factors that guide the sponsor in selecting appropriate methods and timing for the assessment. The purpose of this chapter is to explore how these factors form the basis for a testing algorithm whose objective is to balance the expenditure of time and resources against the need for information at each step of the development process.

### 2. General considerations

In addition to the factors of CNS access and interaction with known targets associated with abuse, several other considerations may inform a decision of the timing and extent of an abuse liability assessment.

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2.1. Therapeutic indication and patient population

The indication under study may in several ways influence the risk of abuse in the marketplace, especially for psychotherapeutic agents. Compounds identified as potential treatments for the anxiety disorders, insomnia, narcolepsy, attention deficit hyperactivity disorder, or pain may be subject to early or more extensive experimentation by substance abusers when the drug is marketed, because some marketed compounds for these therapeutic areas are controlled substances. Additional scrutiny and a lower threshold for conducting a more complete assessment of abuse liability are warranted for new chemical entities, particularly if the drug has demonstrated subjective properties during clinical trials that may be of concern (e.g. sedation, stimulation, euphoria).

As multiple special patient populations may ultimately be exposed to the medication when it is marketed, consideration of how these populations might differ in their susceptibility to abusing the substance is indicated. As specific and validated methods for direct evaluation of abuse potential in special populations are not available, this consideration generally involves extrapolation from available datasets and review of surveillance results. For psychiatric disorders in particular there is a strong and widely accepted association with licit and illicit drug dependence (Kessler et al., 1994; Sacks, 2000; Kandel et al., 2001). The elderly, pregnant and post-partum women, and patients with renal and hepatic impairment may be more susceptible to the adverse health consequences of substance abuse. Compounds targeted for primary or frequent use in these populations may require a more extensive assessment if any results suggestive of abuse liability appear during the development program. Medications targeted for use in children or adolescents pose special challenges, as the risks of exposing these patients (and potentially their family members) to abusable substances are unknown. There are as yet no universally accepted models of addiction in the developing animal, and psychometric instruments for assessing abuse potential in younger patients have yet to be validated.

There is relatively little scholarship on the risks of creating drug-seeking behavior (i.e. iatrogenic addiction) in patients treated with controlled substances. An often cited study by Porter and Jick (1980) suggested that patients treated as inpatients with opioid analgesics were unlikely to develop problems of addiction. Moreover, the perceived risk for benzodiazepine abuse is thought by many experts to be amenable to appropriate clinical management, even over long periods of treatment (Uhlenhuth et al., 1999). However, other data suggest a higher likelihood of medication misuse by patients with a history of opioid or alcohol abuse (e.g. Dunbar and Katz, 1996). It is easy to forget that substance abusers and former substance abusers are also a legitimate patient population for medications that are controlled substances. Appropriate labeling is helpful in informing health care professionals as to the risks of misuse and diversion of a particular compound when prescribing to such high risk patients. Finally, chronic under-prescription in certain populations, such as pain patients and anxiety patients, can lead to a form of drug-seeking behavior known as ‘pseudoaddiction’ (Weissman and Haddox, 1989). For new drugs in development that will likely be scheduled, it may be advisable for sponsors to work with professional organizations and state medical boards to promote treatment guidelines aimed, in part, at minimizing under-prescription that results from fears of regulatory scrutiny (Joranson et al., 2002).

The ultimate clinical setting and context for use of the compound once marketed should be considered. In the clinical trials setting, greater restrictions are typically placed on access to medication and the context for its use than when the compound is marketed. For example, social drinking, cigarette smoking, and the legitimate use of multiple prescription medications by patients are common in the marketplace, but are often restricted during clinical trials. These and other differences may impact upon either the degree to which a compound is abused or the adverse health consequences of abuse (Mitchell et al., 1994; Griffiths et al., 1974 Bigelow et al., 1976; Babor et al., 1978).

2.2. Intrinsic properties of drugs

Information related to the intrinsic properties of the test agent will likely be among the first data available to evaluate the potential for abuse liability. If novel compounds have affinity for known targets of abused drugs and display qualitatively similar intrinsic efficacy, more advanced in vitro and in vivo tests can be used to predict rewarding aspects of the compound under physiological conditions. Such techniques can be used to provide a preliminary estimate of potency and can identify dissociations between binding affinities and functional effects. However, relative efficacy from in vitro models does not always match that measured using in vivo models. Therefore, apparent efficacy in animal models predictive of abuse potential must be compared with apparent efficacy in models predictive of therapeutic effects. These efficacy relationships may be shifted under conditions that diminish therapeutic activity (such as drug tolerance) (Bergman et al., 2000) as well as by the design of low efficacy agonists, as has been suggested for the development of GABA partial agonists (Stahl, 2002). Activity-dependent efficacy may also differentiate the properties of a test agent under diseased versus normal conditions. For example, the uncompetitive NMDA open-channel blocker, memantine, is proposed...
to be associated with less toxicity than traditional channel blockers due to its rapid blocking and unblocking rates and activity only when the channel is open for pathological periods of time (Le and Lipton, 2001). Activity dependence can be measured using in vitro electrophysiological models and in vivo disease models in animals.

The selectivity of the pharmacological profile is another key consideration for abuse liability. For example, while efficacy at mu opioid receptors might raise an immediate concern, additional activity at kappa opioid receptors might mask or counteract the mu activity, as kappa receptors are more frequently associated with producing a dysphoric state (Kumor et al., 1986; Pfeiffer et al., 1986). Thus, while compounds with multiple actions may have an increased potential of activating a target predictive of abuse liability, an overall pharmacological profile including other subjective or untoward actions may under some circumstances mitigate this risk.

The exposures at which effects predictive of abuse potential are measured, as well as the therapeutic window, must be carefully considered. Compounds developed for their highly selective affinities may activate undesired, lower affinity targets when tested at concentrations or doses many fold greater than those intended for therapeutic purposes. If effects in animals suggestive of abuse liability are seen only at concentrations well above (>10-fold) those expected to be therapeutic in humans, then patients might be less likely to experience the reinforcing properties of the medication, even when used at doses somewhat higher than recommended. Nevertheless, this scenario suggests the need for more extensive animal testing, because lower tolerability may prevent testing of these high exposures in humans.

Test agents with novel mechanisms of action pose risks of abuse potential that are entirely unknown. Human and animal receptors can differ in structure, binding affinity and signal transduction mechanisms that may have important consequences for abuse potential. This may be particularly relevant for novel targets, where relatively less information is available to provide context for the results. Screening for interaction with known receptors and transporters may not necessarily reveal a potential problem if the target with which the compound interacts represents an undiscovered mechanism for drug reinforcement or physical dependence. This reflects a limitation of in vitro screening against known targets of abuse liability and highlights the importance of testing the compounds with novel mechanisms using in vivo paradigms. Depending on the sensitivity of the animal models to detect subtle pharmacological differences, information on the risk of abuse potential may come only from clinical development programs.

2.3. Pharmacokinetics

Several pharmacokinetic issues should be considered in evaluating the abuse potential of a new compound. First, the rapidity and extent of absorption and brain penetration can affect the quality of the drug’s likely subjective effects independently of its pharmacological mechanism of action. Rapidly absorbed drugs that enter the CNS quickly are generally associated with a greater likelihood of abuse than more slowly absorbed drugs (Mumford et al., 1995; Stitzer and de Wit, 1998).

Drug elimination and metabolism may also play an important role. Depending on the route of elimination, exposure (and thus abuse or dependence potential), may be increased in hepatically or renally impaired or geriatric patients. Compounds metabolized primarily by enzymes, such as CYP2D6, for which there are both slow and fast metabolizers, may show substantial (10-fold) inter-individual differences in peak plasma concentrations (C
<sub>max</sub>) or total exposure (AUC). Thus, the slow-metabolizing population could be at altered risk of abusing a substance, if it has abuse potential. Similarly, compounds metabolized primarily by an enzyme (e.g. CYP3A4) that might be susceptible to metabolism inhibition by the co-administration of another medication may show similar large increases in C
<sub>max</sub> or AUC, and a corresponding alteration in abuse potential. CYP3A4 is also differentially expressed in men and women (Harris et al., 1995; Gorski et al., 1998); such a variation in enzyme abundance can modify the metabolism of a drug like levo-alpha-acetylmethadol and, therefore, affect its pharmacodynamics and toleration (Oda and Kharasch, 2001; Schnoll, unpublished observations). Other forms of drug interactions may alter dissolution rate, gastric emptying or protein binding and thus modify either the drug’s acute subjective effects or change its rate of elimination (Sellers et al., 1989). These changes in biotransformation and elimination could also affect the intensity of an abstinence syndrome produced by the drug. Modern drug development programs typically conduct extensive studies of drug interactions for safety purposes, and these data can be valuable in monitoring for risks of abuse liability or dependence. Finally, species differences in drug pharmacokinetics can influence the interpretation of preclinical evaluations of reinforcement and physical dependence (Kreek, 1979; Garrido and Trocóniz, 1999).

The pharmacological activities of major metabolites should also be reviewed. Metabolites that are more active at CNS receptors associated with abuse potential may increase the risk of abuse of the parent drug. Sibutramine (Meridia®) is an example of a drug with active metabolites at the dopamine transporter (Sibutramine summary basis of approval, 1997; Meridia® package insert, 1999); this activity may have been responsible for its control under the CSA. The abuse
potential of a metabolite may be mitigated if the metabolite appears only long after drug administration. The analgesic tramadol, for example, has only weak affinity for the mu opiate receptor; however, the O-demethylated (M1) metabolite has substantially higher affinity for mu receptors than parent drug (Gillen et al., 2000). M1 contributes to the analgesic activity of tramadol (Valle et al., 2000) and may contribute to its subjective effects. As with other safety assessments, there may be a unique human metabolite, not present in the animal species chosen to assess abuse potential. If this occurs, preclinical studies may need to be repeated in an alternative animal species, or the metabolite may need to be synthesized and tested in the standard animal species. Alternatively, more weight may need to be placed on any potential signals of abuse liability in humans. Substantial increases in $C_{\text{max}}$ and AUC due to pharmacokinetic factors may also increase the potential public health consequences of abuse, if administration of doses substantially above therapeutic does is associated with significant functional impairment (e.g. sedation, motor incoordination, disinhibition) or medical disability (e.g. respiratory depression, stroke, or cardiac arrest).

2.4. Drug formulation

Advances in the pharmaceutical sciences have resulted in the availability of products with new routes of administration and altered duration of action. These technologies may permit the development of drugs with otherwise unacceptable physical characteristics or pharmacokinetics, and also have allowed the re-introduction of existing drugs with enhanced pharmaceutical performance. Improved performance of the dosage form can result in benefits to safety (e.g. blunted $C_{\text{max}}$), or compliance (e.g. less frequent dosing).

A drug’s pharmaceutical properties may also directly influence its potential for abuse or physical dependence. For example, the time to onset of subjective effects can directly affect the perception of drug liking. A study by Mumford et al. (1995) examined the effects of immediate-release and extended-release formulations of alprazolam in subjects with a history of sedative–hypnotic abuse. The immediate-release formulation produced higher ratings of positive drug effects and a greater estimate of ‘street value’ in these subjects, leading the authors to conclude that the longer acting form had less liability for abuse (probably due to differences in release rate). Similarly, the combination of onset of action and system of drug delivery most likely underlies the reportedly low abuse potential of dronabinol, the orally administered form of delta-9-tetrahydrocannabinol (Calhoun et al., 1998).

The data supporting a role of formulation in the abuse liability of prescription drugs suggest that an analysis of the active pharmaceutical ingredient (‘drug substance’) cannot fully predict the abuse liability of the final drug product. For this reason, it is of value to study the drug’s subjective effects using the final dosage form that will be advanced for marketing approval, although unfortunately all methods of product manipulation cannot be predicted. A drug’s formulation can often influence the setting in which it is used and thereby the population who has access to it. As mentioned earlier, drugs formulated for inpatient use may primarily be abused by health professionals. Drugs formulated for special conditions may present unique challenges for abuse potential assessment due to the nature of the exposed population and unusual dosage form. For example, oral transmucosal fentanyl citrate is a palatable delivery system effective in breakthrough cancer pain and for pediatric sedation (Epstein et al., 1996; Portenoy et al., 1999). The potential for abuse of such novel dosage forms is not clearly understood and may benefit from the development of new assessment instruments and experimental designs.

Despite the considerable care exercised by sponsors wishing to provide a tailored method of drug delivery, it is known that such formulations can be circumvented by those who want to abuse them. This may result in abuse of a form that is radically different than the approved formulation: a tablet, capsule or ingredients in a patch may be dissolved in liquid and injected; an extended release preparation may be altered to have all the drug released in a single bolus; an oral formulation could be crushed or the powder removed from a capsule and insufflated; or the powder or liquid could be placed on tobacco and smoked. The modifications of an approved formulation for abuse depend on the ingenuity of abusers to try different approaches until one or more achieve the anticipated goals. If a product is scheduled under the CSA or is known to have subjectively identifiable CNS effects, it can be anticipated that attempts will be made to modify the formulation to increase the reinforcing effects desired by the abuser. Once this is accomplished, the information will be widely transmitted via the internet and other media. It is important that sponsors attempt to anticipate these forms of experimentation, monitor for their appearance, and institute remedies when possible. An example of such a remedy is the addition of an antagonist to an orally administered agent to reduce intravenous use. The earliest example of this approach was the addition of naloxone to preparations of the narcotic analgesic pentazocine in response to the ‘Ts and Blues’ phenomenon of the late 1970s. After the addition of naloxone, abuse of pentazocine (as measured by DAWN mentions) declined steeply (Baum et al., 1987), although other explanations for the decline cannot be ruled out due to the lack of controlled studies (Reed and Schnoll, 1986). Surrupitious administration of drug to an
unsuspecting person represents another method by which dosage forms have been circumvented. This phenomenon was reported with the benzodiazepine hypnotic flunitrazepam, a drug not approved for use in the US (Schwartz et al., 2000). At the request of European regulators, the formulation of the recently approved hypnotic zaleplon was modified with colorants to prevent the drug from being disguised in a beverage and covertly administered to others (EMEA, 2000). It is likely that the formulations of future sedative–hypnotics of similar pharmacology will be designed in this way.

Combination products in which one drug confers greater risk of toxicity than the abusable drug or acts as an antagonist to the abusable drug may reduce abuse but may result in greater toxicity than the single product. Acetaminophen in high doses is hepatotoxic, which is not true of codeine or hydrocodone, and naloxone or naltrexone in a product could result in precipitated withdrawal in patients who are legitimately using the product. Acetaminophen in high doses is hepatotoxic, but may result in greater toxicity than the abusable drug or acts as an antagonist to the abusable drug may reduce abuse greater risk of toxicity than the abusable drug or acts as an antagonist to the abusable drug may reduce abuse. Sheet the compound through the same molecule (e.g. D2/5HT2A antipsychotics). Thus, the risk of abuse liability for new drugs—or even the process by which they should be evaluated—cannot always be ascertained simply through identification of their molecular targets.

If a product is subject to abuse, sponsors should be prepared to determine if the product can be synthesized from over-the-counter medications or easily available chemicals, and if such a synthesis is possible in a home laboratory. Sponsors should also give consideration to the more likely approaches abusers may take in manipulating the product.

The ability to anticipate all the potential forms of manipulation to produce abuse will be difficult. As new delivery systems are developed, abusers will make every effort to learn how to release the abusable ingredient as easily and cheaply as possible. Delivery systems that are the most beneficial to the patient (extended release systems) may become the most desirable to the abuser because of the large amount of drug in each dosage unit. Finally, it will be necessary to determine the extent to which potential or even real abuse should be allowed to interfere with the needs of the legitimate patient who derives benefit from appropriate use of the medication.

3. Approaches to identify and test drugs needing evaluation

A number of preclinical and clinical methods have been developed to help characterize abuse-related effects of drugs. The technical details of such methods are outside the scope of this article and are described elsewhere in this volume. However, application of these techniques in the right order and at the right time is critical to best apply limited resources (staff, money and compound) and to ensure that the necessary information is available at key decision points. Because every compound and every program is unique, abuse liability testing may not follow the same course in all cases. Staging these tests requires an understanding of the considerations mentioned earlier in this article and of relevant regulatory guidances.

If a new drug in development shares clear structural or biochemical similarities to known drugs of abuse, then its evaluation for abuse liability can be accelerated accordingly. However, as discussed earlier, advances in molecular sciences have afforded the development of completely new classes of drugs belonging to novel families of receptors and other protein targets. In addition, established classes of drugs are being manipulated to alter their selectivity within or across families of targets, with some programs focusing on multiple targets in the same molecule (e.g. D2/5HT2A antipsychotics). Thus, the risk of abuse liability for new drugs—or even the process by which they should be evaluated—cannot always be ascertained simply through identification of their molecular targets. A rational process of screening, analogous to algorithms used to discover and develop new drugs, may be used to shepherd the compound through the evaluation at a level of intensity consistent with its overall developmental stage and the perception of risk at the time. It should be acknowledged that abuse-related properties of novel drugs may not be readily identified by methods developed to characterize known drugs. Furthermore, phenomena that resemble abuse-related effects may not be related to drug abuse at all; for example, antihypertensives and selective serotonin re-uptake inhibitors have been reported to produce discontinuation phenomena in some patients, but these events have not been linked to abuse potential (Price et al., 1996; Webster and Koch, 1996). Therefore, it is important to provide measures in later stages of development that are sensitive enough to detect a potential problem prior to filing a registration dossier. This section outlines preclinical and clinical factors that may assist in rapidly and accurately identifying the risk of abuse, and provides a general framework for orchestrating the overall process.

3.1. Preclinical detection

Evaluation of a compound’s potential for abuse is based on data relating to the chemistry, pharmacology (preclinical and clinical), pharmacokinetics, and pharmacodynamic profiles of the drug and adverse events/effects (Klein et al., 1999). This includes determination of the drug’s receptor binding affinities, functional activity at the cellular level, preclinical pharmacology, reinforcing efficacy, discriminative stimulus effects,
potential for physical dependence and pharmacokinetics as outlined in the early stages of the Testing Algorithm (Fig. 1). Preclinical animal testing has value in predicting reinforcement and dependence in humans and offers significant advantages that facilitate progress through the decision tree. Animal models can be employed very early in development programs—even before an IND is filed—and can include comparisons with other drugs that are not approved for human use. Higher doses and more stringent dosing regimens can be studied in...
animals, including assessment of exposures well above those required for efficacy. The results can thus be used to help choose compounds that may progress to more demanding clinical studies. In addition to development candidates, metabolites and precursors can also be evaluated. Parenteral routes of administration such as intravenous infusion or minipump delivery can also be utilized. If pharmacological antagonists are available, they can be used to probe mechanisms of action and to precipitate withdrawal. Taken together, animal tests of abuse liability can be of significant value to sponsors because they can be conducted earlier and more cheaply than human assessments, and also because they yield unique information.

Abuse liability testing in standard laboratory animals consists of behavioral protocols that model various aspects of drug seeking/taking, subjective properties, and physical dependence-producing effects. The direct reinforcing effects of drugs are measured using self-administration paradigms in rodents and nonhuman primates. Typically these studies are conducted with intravenous drug delivery, although occasionally oral administration is studied based on solubility or other factors. While the rapid delivery to the CNS by the intravenous route sets up optimal conditions for a positive signal, abuse of medications often involves this route. On the other hand, a positive signal under these conditions may overestimate the reinforcing potential of an oral drug, especially if its pharmaceutical properties do not easily lend themselves to parenteral administration. Intravenous self-administration experiments are typically conducted in animals trained to self-administer a known reinforcer. Traditionally, there has been very good concordance between drugs that support self-administration in laboratory animals and those that are self-administered by humans (Johanson and Balster, 1978). False negatives include indole-based hallucinogens and cannabinoids that do not readily support self-administration in animals. False positives include some drugs in the anti-histamine class (e.g. Beardsley and Balster, 1992). The selection of appropriate testing conditions will be aided by pharmacokinetic data that will typically be available early in the development program. As with drug discrimination and dependence studies described below, the pharmacokinetic information will allow an approximation of target exposures both within and above the expected (or perhaps known) efficacious plasma concentrations. In general, self-administration studies conducted in nonhuman primates are thought to reflect most closely the human potential for abuse. However, rodent studies can offer the advantages of requiring animals with less drug experience, ease in performing invasive neurobiological manipulations and the opportunity to examine knockout and transgenic animals. Species differences with regard to the target of interest must be taken into consideration.

A second commonly used procedure employed for abuse liability testing is drug discrimination (Balster, 1990; Brady et al., 1990; Colpaert, 1999). The underlying premise of this model is that drugs are abused in part because of their subjective effects and that agents that produce internal cues similar to abused substances may also have the potential for abuse. The sensitivity and selectivity of drug discrimination depends on the training conditions selected; these should be made with care, especially for novel compounds, because it may not be clear what the reference drug should be. Drug discrimination data may be particularly important for drug classes where self-administration does not occur in animals or only occurs under special conditions that are not easily reproduced.

Other, though more indirect, methods for assessing abuse liability are the conditioned place preference procedure (Tzschentke, 1998; Bardo and Bevins, 2000) and locomotor behavior (Woolverton et al., 1994). Because these procedures require minimal training in comparison with self-administration and drug discrimination, they can be used to get an early read on potential liabilities and avoid delays that can be associated with the more technically demanding procedures. As with the other behavioral models the training conditions can influence the results.

Neurochemical data, especially when collected in vivo, can be especially valuable. There has been much research into the neurobiological substrates of abused substances and the mesoaccumbens dopaminergic system has been identified as an important modulator of reinforcing stimuli including drugs (Everitt and Wolf, 2002). Microdialysis experiments aimed at revealing the neurochemical correlates of drug actions can be used to assess the need for further abuse liability testing.

Chronic administration of certain agents can produce physical dependence and withdrawal following cessation of drug treatment. Assays for evaluation of these properties of test agents include increased sensitivity to seizures (induced electrically or chemically), manifestation of observable behaviors (e.g. weight loss, wet-dog shakes, writhing, motor inactivity) or disruptions in trained behaviors (e.g. operant responding, increases in self-stimulation thresholds) that are associated with removal of the drug (spontaneous withdrawal), or precipitation by injection of an antagonist (e.g. Aceto et al., 1994).

The rapid advancements in the area of molecular biology have greatly expanded the tools available for investigating the molecular targets of various behaviors (Nestler, 2000). The creation of a knockout mouse is often part of target validation for early stage discovery projects and also can provide an indication of potential toxicities associated with the elimination of a particular
circuit element (i.e. the ultimate antagonist). The processes of tolerance/dependence and withdrawal can be studied by comparing administration of the drugs known to have liabilities or the test article in knockout versus wild-type mice. The creation of knock-in mice possessing genes with mutated sequences is also a useful technique. Even a single amino acid change can alter the biological function of a receptor and can be used to dissect the contribution of a particular receptor subunit to behaviors associated with abuse potential.

Finally, sponsors will benefit from examination of data not specifically collected for the abuse liability assessment. Not all drug developers have the capabilities in-house to perform the special assessments described in this section. Contracting them out can be a laborious and time-consuming process. Examination of spontaneous behaviors, effects on physiological systems (e.g. sympathetic responses), and results from in vivo efficacy models may all be of value in deciding whether more testing should be conducted.

3.2. Clinical detection

While animal studies often provide some indication of abuse liability, clinical data are usually the most important indicators of whether or not a drug will actually be abused. For a compound in early clinical development that has shown no properties similar to those of abused drugs, detection of abuse liability can be difficult. If any data suggestive of abuse liability are generated in animals or during the clinical development program, human laboratory based assessment will be required. Formal human laboratory based assessments of abuse liability have been refined by many years of experience. All of these assessments focus on self-report of the subjective experiences elicited by the drug. In addition, choice procedures may also be employed. Because the laboratory assessments play a prominent role in the section of the marketing application dealing with abuse liability (particularly for new chemical entities), the design of these studies should be carefully considered. Typically, the human laboratory studies occur later in the development process, when the therapeutic dose range is understood, the important adverse events have been identified, and the major features of the final dosage formulation have been determined. However, an earlier evaluation may be warranted if the preclinical data suggest a significant clinical or business risk, and the added time allows further experiments inspired by lack of clarity in the results or desire for additional information. Some programs may require preliminary scholarship or consultation with experts if the drug does not fall into an established pharmacological class or belongs to a class without a clearly defined methodology for evaluating abuse liability. For example, neuroprotective agents with activity at glutamate receptors may be difficult to evaluate because of the lack of validated measures for this class, difficulty in selecting the appropriate subject population and positive control, ethical issues related to informed consent, and other factors (Klein et al., 1999; H. de Wit, unpublished presentation).

The best indicator of abuse or the lack of abuse may come from other countries if the drug has been approved outside of the US. Should there be evidence of abuse, sponsors should be prepared to incorporate measures of abuse-related activity into their clinical programs as well as to conduct the full spectrum of preclinical and clinical laboratory studies. Lack of evidence of abuse in other countries may reduce the possibility that the drug will be abused in the US, but does not eliminate it entirely. Because trends in drug using habits may vary from one country to another, and differences in genetic makeup may alter sensitivity to the euphoria-inducing or toxic properties of a drug, tests in a domestic population of patients and drug-experienced subjects will be of greatest value. As with the preceding considerations, consultation with FDA is important to ensure that the key aspects of study design are suitable for regulatory purposes.

Other sources of clinical data can be very valuable in influencing the timing and direction of the abuse liability program. In Phase 1 and early Phase 2, entry criteria are usually restrictive, excluding patients for many reasons. Known drug or alcohol abusers are seldom allowed to participate in clinical trials at this early stage in development. Thus, patients in these initial clinical studies are not likely to provide clearly interpretable signals of abuse liability. However, data in these early studies can sometimes identify events reflective of abuse liability or physical dependence. Characterization of the adverse event profile, for instance, may reveal positive mood changes or discontinuation emergent signs and symptoms (DESS). Evidence of such events, or suspicion that they might occur, may inspire incorporation of elements into clinical protocols designed to measure them more accurately. These elements might take the form of an additional psychometric measure (e.g. profile of mood states), a physiological parameter (e.g. heart rate, blood pressure), a psychomotor performance test, or a blinded washout period in conjunction with a validated withdrawal instrument (e.g. Physician Withdrawal Checklist). Any single sign or behavior may not be sufficient to trigger extensive further investigation; it may take specific combinations of events or a scoring system to indicate when further studies are needed. Additional events of interest throughout the clinical program are reports of spontaneous euphoria, sedation, cognitive and/or motor impairment, appetite alteration or sleep complaints. Other indicators may occur only when subjects are given very high doses. Euphoria elicited at such high doses may be a signal that abusers
will try to obtain large doses that they can administer for
the high, and therefore, be at risk for adverse events
considered unlikely at the recommended clinical expo-
sures. In larger trials, when monitoring is decreased and
the population more diverse, behavior of subjects can be
analyzed to determine if they are taking more drug than
prescribed, seeking drug from other subjects, willing to
pay for additional drug, or wanting to continue on the
drug after the trial is completed. Registries of patients
who continue on the drug after completion of the trial
should be monitored closely for reasons they wanted to
continue on the medication and for their behavior
during the continuation phase. Another important
consideration is the individual's genetic predisposition
toward substance abuse (Kendler et al., 1997). If a
person were to be genetically predisposed to abuse drugs
but have no such behavioral history, ethical considera-
tions may preclude testing in that individual for fear of
precipitating a drug abuse disorder. Individuals with no
history of abuse or known genetic predisposition are
often excluded from studies on abuse because of the
potential they may become abusers, although this
potential is low. This is why subjects with clear histories
of abuse are usually preferred in such studies. Overall, it
is important that enough empirical information be
collected to support the sponsor's scheduling recom-
mandation in the US marketing application.

If abuse liability is a consideration for any investiga-
tional drug, Phase 4 commitments will likely be required
to evaluate the emergence of drug-seeking behavior in
the general population. Generally, sponsors should
expect to track instances of diversion or misuse through
proactive forms of surveillance and to institute a risk
management plan (Cicero et al., 1999). One obvious
form of risk management is scheduling under the CSA;
however, there are other interventions that may assist in
limiting use of the drug to the intended population, such
as educational programs, special storage conditions,
patient registries, or studies in vulnerable populations
(e.g. Knisely et al., 2002).

3.3. Potential testing algorithm

One potential example of a decision tree analysis of
abuse liability testing is presented in Fig. 1. Not
intended as a model for all programs, it is provided
rather as a general guide of testing procedures available
and how they might be coordinated in the context of
industrial drug development. As indicated in the figure,
if the compound is determined not to enter the CNS
then further testing should not be necessary unless
additional data suggesting abuse potential come to light.
If the drug does enter the CNS, a comprehensive set of
binding assays may be performed to analyze its interac-
tion with known targets of abused drugs. This type of
binding panel is readily available though contract
laboratories and is typically performed by sponsors in
their effort to document selectivity of the drug. How-
ever, a binding assay alone cannot predict activity
consistent with that of an abused drug. Therefore,
assays intended to measure the functional effect of the
drug on CNS neurons is also of value, and such assays
will also help to determine the intrinsic activity of a
compound that produces a signal in one of the binding
assays (i.e. agonist, antagonist or partial agonist). These
two pieces of information will inform a decision as to
whether in vivo characterization should be carried out.

Even if the above tests do not indicate a risk of abuse,
sponsors will normally collect a substantial amount of in
vivo data prior to IND filing. For example, the safety
pharmacology studies recommended under Interna-
tional Conference on Harmonisation (ICH) guidelines
(Food and Drug Administration, 2001) include an
assessment of spontaneous behaviors that may reveal
evidence of an abuse-related effect. If the drug is being
developed to treat a psychiatric condition, then data
from animal models used to advance the compound may
be useful in assessing abuse-related activities.

If evidence of abuse liability is discovered in these
preliminary tests, in-depth animal studies are usually
advisable. These procedures are well documented in the
literature and are discussed in FDA’s draft guidance on
abuse liability assessment (unpublished draft). An
appropriate time to conduct these studies is in the
earlier stages of clinical development, preferably before
the “End of Phase 2” meeting with the review division
and the Controlled Substances Staff. This will allow
regulators to monitor the progress of the investigation
and offer comment on the design of additional studies.
As noted in the algorithm, flexibility in the decision tree
may be justified depending on individual circumstances.
For example, if a compound were to act as a functional
mu opioid agonist in vitro yet show no evidence of
agonist activity in preliminary in vivo tests, then testing
in formal animal models might still be considered.

Justification for an abuse liability investigation may
arise from events noted during the clinical program, as
noted earlier. These events are themselves part of the
assessment package, but may also inspire preclinical and
clinical studies even in the absence of known chemical,
biochemical or behavioral evidence from the preclinical
program. Spontaneous findings from AE reports or
questionnaires also represent important information to
discuss at the End of Phase 2 meeting with regulators.

Formal laboratory studies of abuse liability in hu-
mans will typically occur later in the program, but might
be accelerated if the need for one is obvious or if the
results would help inform a business decision. Having
the animal data available will be helpful in designing
studies focused on subjective effects, as well as those
that might involve motor or cognitive performance.
Finally, an assessment of the chemical and physical
properties of drug substance and drug product is valuable to assess the risk of circumventing the intended route of administration, or of illicit synthesis. These analyses are best performed late in the program, when the commercial dosage form has been established. Again, flexibility to this decision tree may be indicated if the goal of the development program is to create a new dosage form of an existing medication.

4. Summary and conclusions

This chapter has reviewed several of the factors that industrial sponsors would be advised to consider when developing a drug with activity in the CNS. Apart from the obvious characteristics of chemical structure and primary pharmacology, sponsors need to attend to the compound’s secondary activities, metabolism, formulation, and intended clinical population. Each of these factors can substantially modify the drug’s ultimate risk of illicit diversion, physical dependence, or other unintended consequences related to drug abuse. Some form of assessment will clearly be needed for new agents, not only for the purposes of inclusion into the marketing application, but also to inform the development organization as to the safety and business risks posed by a compound likely to be scheduled under the CSA. This chapter proposes some possible methods and routes by which the assessment can be staged; however, all projects are unique in some way and flexibility will be needed. It is also advisable to consult regulators at all major development milestones to ensure that the amount and quality of information is sufficient for a scheduling determination.

Despite the availability of testing methods and a rich history of scholarship on the measurement of drug abuse related phenomena, several limitations still exist that pose challenges to an effective assessment of abuse liability. It should be recognized that false negatives and false positives can be identified in both animal and human models of reinforcement and liking, respectively. In animal procedures, there is typically a primary outcome that can be clearly interpreted, but confusion may arise when different animals produce opposite results or if the signal from the test agent is greater than vehicle but less than the reference drug. Similar outcomes can occur in human studies with the additional complication that multiple dependent variables are recorded. These multiple variables can produce conflicting results, especially with a test substance that differs greatly from the reference drug. Other challenges exist in the clinical evaluation of abuse liability, including difficulties in arriving at equivalent doses between test and reference drug, constraints of the experimental setting, limited access to patients in the context of a clinical trial, and lack of experimental methods to study formulation tampering. Collectively, these limitations are responsible for continued uncertainty around product approval, labeling, and commercial attractiveness.

To some extent, a lack of standardization separates abuse liability from other specialty areas of research that are routinely used for the support of marketing applications. Abuse liability testing typically occurs in a small subset of independent academic laboratories with special training and a primary emphasis on basic research. As a result of this arrangement, a diversity of procedures, data capturing methods, psychometric instruments and statistical analyses are used. Studies of the abuse potential of new CNS-active agents would produce more useful information if there were agreement on standard methods that could be reproduced in any laboratory. Such an agreement would lead to uniform quality of information from one regulatory submission to another. The conduct of these studies would benefit from following Good Clinical Practices (GCPs), as do other industry-sponsored trials. This would in turn assist sponsors in preparing for marketing applications outside the US; methods and data analysis techniques that are accepted worldwide would decrease the need to repeat studies and increase the chances of consistent labeling across international markets.

New research intended to address these practical issues will be helpful in minimizing the limitations discussed above. For example, a greater number of drug classes can be tested in standard models and a composite of their effects compiled; additional methods can be developed to bridge the gap between admittedly artificial laboratory studies and real-world clinical practice; protocols can be devised to gain better surveillance data even prior to product approval. The issue of appropriate subject population for human laboratory studies is particularly worthy of further refinement. Although available data suggest that subjects with a history of recreational drug use are more sensitive to the reinforcing effects of drugs (Roche and Griffiths, 1989), studies using subjects without such a history may better reflect risks to most patients for whom the drug will be prescribed. Such experiments, however, may raise ethical concerns. Finally, a focused attempt to clarify ‘gray area’ results will assist in making wise decisions on protecting the public interest while also maximizing drug access to legitimate patients.

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