Drug abuse liability assessment: taking an integrated approach

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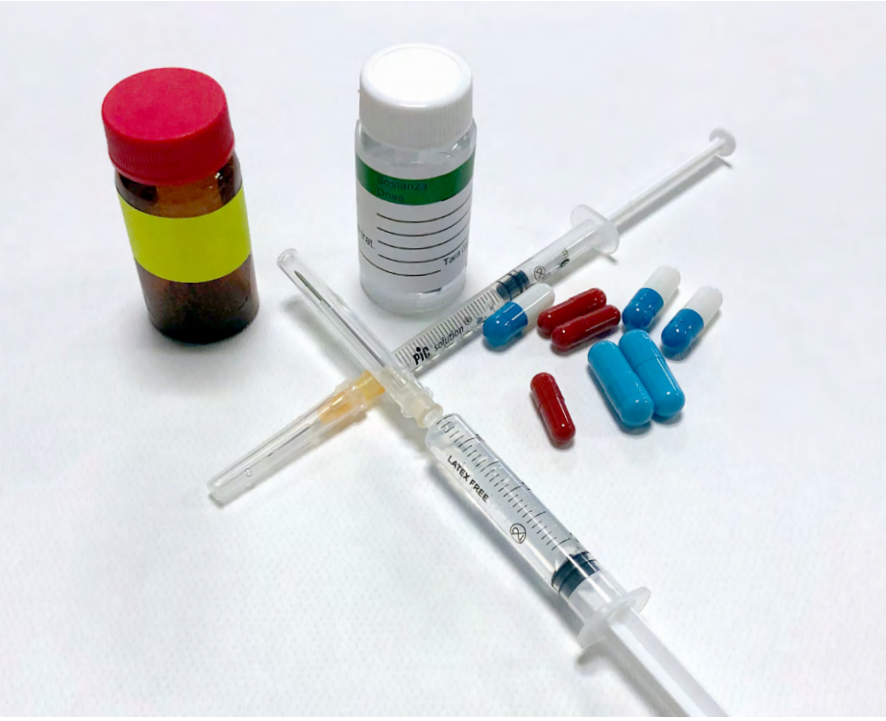

When used as advised by a doctor, prescription drugs have the potential to do a significant amount of good. However, when taken inappropriately, their use can lead to severe adverse events, including, in the case of drugs acting on the CNS, abuse and dependence.

Prescription drug abuse is a growing global challenge affecting the quality of life of millions of people worldwide. According to the National Institute on Drug Abuse, an estimated 18 million people (more than 6 percent of those aged 12 and older) have misused such medications at least once in 2017[1].

The implementation of measures to control the prescribing practices and availability of medicines is the first line of defense against their abuse and misuse. Effective scheduling relies on pharmaceutical developers evaluating the drug's potential for abuse. However, how can this be done in a way that ensures medicines are available to patients as quickly and as cost effectively as possible?

In this article we consider the advantages of adopting an integrated approach to drug development while navigating the regulatory requirements around abuse liability assessment.

THE IMPACT OF SCHEDULING

Any prescription medicine has the potential to be abused, however, drug products capable of producing rewarding psychoactive effects such as sedation, euphoria, hallucinations or mood changes, are considered to be at greater risk of being used recreationally[2]. As a result, new drug applications (NDA) for medications that could affect the central nervous system (CNS) must include an assessment of their potential for abuse.

Assessment of abuse liability not only involves a consideration of a drug's potential for addiction, but a broad range of other factors associated with its potential for misuse, abuse and diversion[3]. These can include the drug's therapeutic indication, availability and ease of synthesis, as well as the potential for negative outcomes resulting from abuse, such as overdose or toxicity. This comprehensive package of information is essential in guiding the decisions of pharmaceutical companies, government agencies, healthcare professionals, and ultimately, the patients who use the product[4].

Abuse liability studies are used by the U.S. Drug Enforcement Agency (DEA) to support their decision to include or exclude the drug into one of five schedules that define the severity of the potential for abuse, and determine the level of control of the drug distribution accordingly (Table 1)[5,6]. These evaluations take into account the medicine's public health benefits, as well as its potential for negative impacts.

Schedule I	– High potential for abuse – Not currently accepted for medical use in the United States – Lack of accepted safety for use under medical supervision	Heroin LSD Marijuana MDMA
Schedule II	– High potential for abuse – Accepted for medical use in the United States or accepted with severe restrictions – Abuse may lead to severe psychological or physical dependence	Amphetamine Barbiturates (e.g. pentobarbital) Cocaine Methamphetamine Opioids (e.g. fentanyl, morphine) PCP
Schedule III	– Potential for abuse is lower than for the drugs in Schedules I & II – Accepted for medical use – Abuse may lead to high psychological or moderate to low physical dependence	Anabolic steroids Barbiturates (e.g. butalbital) Ketamine Marinol
Schedule IV	– Potential for abuse is lower than for the drugs in Schedule III – Accepted for medical use – Abuse may lead to limited psychological or physical dependence relative to the drugs in Schedule III	Benzodiazepines (e.g. diazepam) Other depressants (e.g. tramadol)
Schedule V	– Potential for abuse is lower than for the drugs in Schedule IV – Accepted for medical use – Abuse may lead to limited psychological or physical dependence relative to the drugs in Schedule IV	Opioids in limited quantities and in combination (e.g. codeine, ethylmorphine)

Table 1: Schedules under the Controlled Substance Act

Each schedule has its own measures to control the way in which the drug is manufactured, distributed and prescribed, which are designed to ensure medical availability while reducing the potential for abuse and diversion. These measures directly influence factors such as risk management and the prescription process.

Because of this, scheduling can have a significant impact on the commercial viability of a drug development project. Low scheduling, for example, can free up a drug to be more widely prescribed by physicians to the potential benefit of sales revenues and availability to patients. High scheduling, on the other hand, may delay projects while scheduling is negotiated with authorities, and result in associated financial implications. As a result, a good deal of care must be taken when approaching the assessment of abuse liability.

APPROACHING ABUSE LIABILITY ASSESSMENT

Even drug molecules and their metabolites that are not specifically designed to target the CNS must be assessed for abuse liability if they cross the blood-brain barrier.

When planning for abuse liability assessment, it is recommended that drug developers adopt a two-tiered approach. Here, an initial strategically designed package of tests to comprehensively characterize the compound and understand its pharmacology should be implemented, followed by preclinical behavioral studies that build a wider understanding of the compound's true abuse potential.

Understanding the pharmacology

An important first step in determining whether a drug has abuse potential involves assessing its structure and mechanism of action (including off-target activity), and comparing it with other relevant molecules such as drugs with known abuse potential, as well as direct market competitors and similar families of therapeutics.

A pharmacokinetic assessment should also be made to investigate the drug's blood-brain barrier permeability and relative distribution in the brain. Furthermore, receptor binding studies of the drug and its major metabolites, as well as second messenger system studies, should be used to determine whether the administration of drug may result in psychoactive effects. Data from preclinical toxicology studies may also provide precious indications of the drug's abuse potential.

As the bulk of abuse liability assessment is typically undertaken between phase II and phase III clinical trials, reports of excitation or sedation in early phase I studies can give an indication as to whether drugs should be investigated for abuse liability. The analysis of these early indicators will reveal whether it is necessary to investigate the drug further using animal or human studies.

ANIMAL BEHAVIORAL STUDIES

For drugs that have characteristics indicative of a potential for abuse, the next step for developers is to design and perform animal behavioral studies. Here, drug discrimination, self-administration, conditioned place preference and physical dependence studies are used to assess different aspects of abuse liability. Typically these studies are performed in rodents, as recommended by the latest FDA guidance [2].

Drug discrimination

Drug discrimination studies can be used to determine whether a test drug produces interoceptive effects similar to those of a known drug of abuse. Drug discrimination is not a direct measure of abuse liability; it depends on an animal's ability to identify the subjective interoceptive effects associated with the training drug, which can be positive, negative or neutral [7].

For this reason, generalisation with an active substance known to cause dependence in itself is not necessarily indicative of the potential for addiction. However, drug discrimination procedures can support the choice of the training drug for subsequent self-administration studies.

Self-administration

Self-administration tests are also based on an animal's operant behavior and allow the reinforcing properties of drugs to be evaluated. In this test, animals are trained to respond to a compound with a known abuse potential. The training drug is substituted with the test drug, and a comparison is made. This behavioral experiment has high translational value and a very good predictive validity since there is strong correlation between drugs self-administered by rodents and drugs abused by humans.

Conditioned place preference

Conditioned place preference (CPP) is another approach that can be used to assess a drug's rewarding or aversive effects. Through repeated pairing of a test substance with a compartment of a cage, an animal is conditioned to associate the effects of the drug

with distinct environmental cues, such as the flooring texture or bedding material. An environmental choice test is then performed in the absence of the test substance to determine whether a CPP is observed. In humans, individuals taking therapeutic doses of amphetamine have been shown to develop a CPP for the location in which they consumed the drug[8].

Physical dependence

An essential component in non-clinical abuse liability testing is the evaluation of the potential for a withdrawal syndrome induced by chronic administration, and abrupt cessation, of a test substance. The prolonged interaction of a CNS- active substance with its receptor may induce a series of neuroadaptive responses that may lead to an imbalance of the neurotransmitter systems once treatment is stopped.

The manifestation of physical dependence may vary in intensity and in terms of the symptoms exhibited, depending on the treatment administered, its frequency, duration, as well as individual variability. In rodents, the physiological symptoms of physical dependence are easily measured. However, it is more challenging to evaluate the psychological symptoms that can be investigated using a battery of tests such as movement analysis and other behavioural observations.

General Considerations

There are a number of critical parameters that should be carefully considered when designing animal behavioral studies to investigate the abuse potential of novel compounds. Firstly, given that abuse liability is unrelated to therapeutic use, and that abusers will take a drug by any possible route and reach maximally tolerated doses if necessary, multiples of the clinical effective dose should be tested. Therefore, the dose range evaluated in animals must extend from a therapeutically relevant level to the maximum dose at which an animal remains capable of an operant response or up to doses that produce in animals Cmax levels equivalent to at least 2–3 times greater than the Cmax produced by the highest proposed therapeutic dose, as recommended by FDA guidance[2]. In order to verify that the chosen dose range translates into biologically meaningful exposure in animals, pharmacokinetic determination should be performed alongside behavioral studies. This information will also facilitate the translation of the effects observed in animals to humans.

Another important factor to take into account when designing preclinical abuse liability studies is the choice of the positive control or training drug. This should be a drug with a well-established abuse potential, and if possible, possess similar overall pharmacology and/or be from the same therapeutic area. Should a compound not present obvious pharmacology, comparators from a range of different drugs of abuse schedules should ideally be tested.

HUMAN ABUSE LIABILITY STUDIES

It is unlikely that a full picture of a drug's potential for abuse will be obtained through preclinical studies alone. Clinical abuse liability studies are typically required to complete this assessment, even for drugs perceived to have a low abuse potential.

The evaluation of adverse events in early clinical trials can provide an initial indication of a drug's potential for abuse. The presence of CNS-related effects such as euphoria, mood changes, and hallucinations may be indicative of abuse potential, and typically warrant further investigation.

However, the decision to run human abuse liability (HAL) studies must be carefully considered and will depend on the information obtained during preclinical and early clinical studies. Typically, HAL studies are necessary when abuse related signals are observed and measured in preclinical abuse liability studies or if abuse related adverse effects are observed in clinical studies.

HAL studies are generally conducted in recreational drug users that have a history of using drugs of the same pharmacological class as the test compound, whenever possible. These individuals are recognized as being best placed to evaluate a drug's

effects, as they are representative of the population at greatest risk of illicit drug use, and their prior experience can result in a more meaningful evaluation[4]. Data is collected on the subject's experience of using the test drug, and the extent to which they would take the drug again.

HAL studies can be more time and resource intensive than conventional phase I trials and require specialist expertise. To achieve the most effective results, HAL studies should be carefully planned and well-designed.

BENEFITS OF AN INTEGRATED APPROACH

Because of the length of the scheduling process and the implications drug scheduling can have upon financial return and market access, it is vital that sponsors consider the factors that can impact abuse liability for a particular drug development project ahead of time. Planning for potential abuse liability should ideally begin at the candidate selection stage to avoid unexpected surprises during early clinical trials.

The evidence needed to inform abuse liability assessment should be collected as part of a routine drug characterization program to guide the decision on whether more detailed behavioral studies are required. Taking an integrated approach to drug development breaks down walls between project teams and reduces the risk that key information will be overlooked.

While insufficient evidence around abuse liability can severely impact on drug scheduling, conducting poorly designed studies that produce potentially concerning safety data, even though the compound has no abuse potential, can result in an unnecessarily harsh schedule being applied by the regulatory authority. Subtleties in experimental design can have a significant impact on the outcome of animal and human studies, and care must be taken when designing behavioral studies – with such studies having the unconditional support of the project sponsor and regulatory authorities.

Integrated development programs ensure effective communication between the individual teams working on a development program. Silo thinking can lead to experiments being designed according to 'in-house' procedures, rather than what's best for the program as a whole. But with specialist experts heading up integrated programs from the outset, potential issues can be anticipated and planned for accordingly. Through forward thinking and collaboration, development times can be minimized and the likelihood of success can be maximized.

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CONCLUSIONS

Prescription drug abuse is a growing global challenge that underlines the importance of assessing the abuse potential of pharmaceutical products and implementing measures designed to control their non-medical use. However, given the complexity of the scheduling process, and the experimental subtleties that can impact on preclinical and clinical studies used in part to determine a drug's schedule, it is essential that abuse liability investigations are designed with the utmost care. By adopting an integrated and considered approach in the earliest stages of development, this process can be streamlined, helping to ensure new medicines are available to the patients who need them as quickly and as cost effectively as possible.