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CENTRAL NERVOUS SYSTEM (CNS) ACTIVE DRUGS

Complex Considerations

As you work towards a successful New Drug Application (NDA) submission, there are many considerations that must be taken into account, specifically for CNS-active drugs. Molecules or compounds that are centrally active (the parent drug or metabolite[s]), may require additional evaluations to characterize the drug effects and unique safety characteristics. Not all centrally acting drugs require additional assessments; however, strategic direction early in a drug development program can help determine if such studies should be planned, or may be waived.

The Landscape

CNS-active drugs have certain unique attributes that necessitate additional specialized study:

- Cognitive impairing/enhancing effects
- Reinforcing effects (abuse potential)
- Physical dependency and tolerance
- Additive effects (when combined with drugs and alcohol)

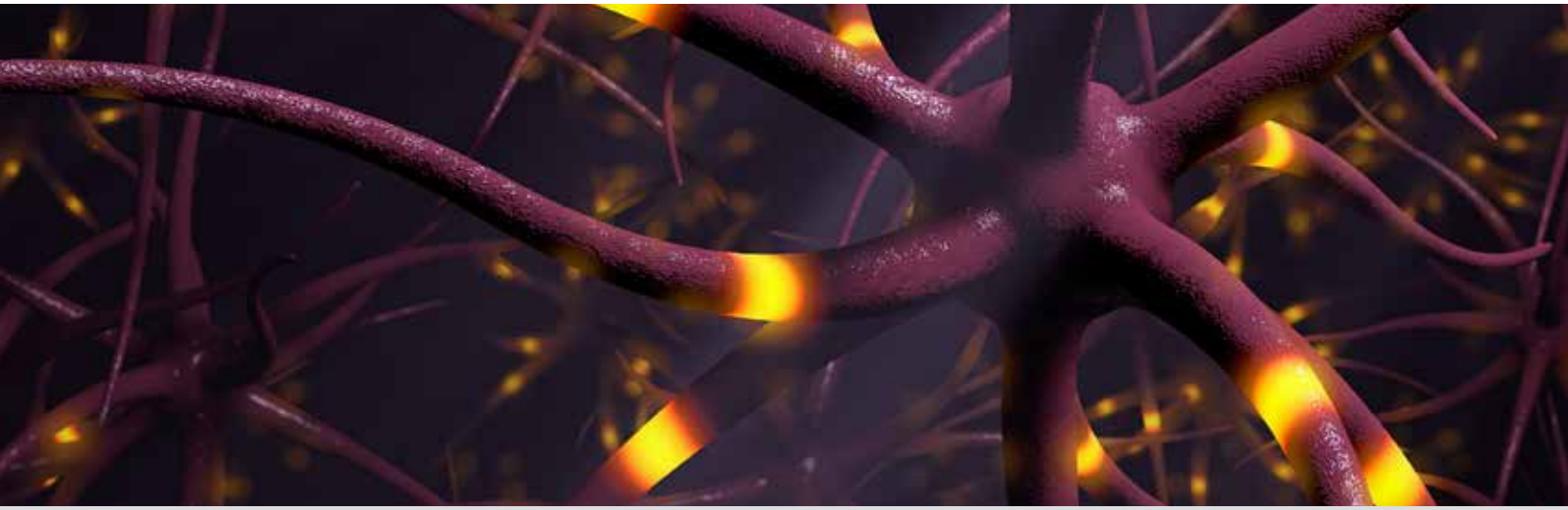
Because CNS-active drugs can have unintended effects in the critical neural system that influences so many aspects of human health, the required preclinical and clinical studies are typically more detailed and rigorous than for other types of drugs. In addition, the results of such studies will have a material impact on your development program going forward, both in terms of timelines and budget, so you will want the answers for yourself as much as for the regulatory bodies.

One of the key considerations in evaluating a CNS-active drug molecule (or its metabolites), is the evaluation of abuse potential. Such data is integral in determining whether or not a new drug approved for medical use may need to be a controlled substance. The FDA uses an eight-factor format for NDA submissions of CNS-active molecules.

Factors determining control under the Controlled Substances Act (CSA) are set out in 21 U.S.C. 81(c), and they are:

1. Actual or relative potential for abuse
2. Scientific evidence of its pharmacological effect (if known)
3. The state of current scientific knowledge regarding the drug or other substance
4. History and current pattern of abuse
5. The scope, duration, and significance of abuse
6. What, if any, risk there is to the public health
7. Psychic or physiological dependence liability
8. Whether the substance is an immediate precursor of a substance already controlled

A controlled substance is assigned a schedule based on whether it has a currently accepted medical use in treatment in the United States, and its relative abuse potential and likelihood of causing dependence. Physical dependence is a neuroadaptive process that can occur in the absence of abuse potential. The ability of a drug to produce physical or psychological dependence plays a role in the scheduling placement of an abusable drug under the CSA.



DRUG SCHEDULING AND THE CSA

The CSA, enacted in 1970, provides a framework for appropriate labelling and controlled distribution of medications with certain attributes. Scheduling of a medication impacts market availability and prescribing behavior. For planning and development purposes, it is important to act on early signals that suggest scheduling will be necessary. Drugs and other substances that are considered 'controlled substances' are classified into five schedules. As the schedule progresses from I through V, the abuse potential reduces and thereby the limitations on prescribing practices are lessened. Schedules I and II both represent drug molecules with the highest known abuse potential. Schedule I drugs are not approved for medical use in the United States, whereas Schedule II drugs are.

The complete drug schedules are presented by the FDA as follows:

Schedule I

Schedule I drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse. Some examples of Schedule I drugs are: heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), 3,4-methylenedioxymethamphetamine (ecstasy), methaqualone, and peyote.

Schedule II

Schedule II drugs, substances, or chemicals are defined as drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous. Some examples of Schedule II drugs are: combination products with less than 15 milligrams of hydrocodone per dosage unit (Vicodin), cocaine, methamphetamine, methadone, hydromorphone (Dilaudid), meperidine (Demerol), oxycodone (OxyContin), fentanyl, Dexedrine, Adderall, and Ritalin.

Schedule III

Schedule III drugs, substances, or chemicals are defined as drugs with a moderate to low potential for physical and psychological dependence. Schedule III drugs abuse potential is less than Schedule I and Schedule II drugs but more than Schedule IV. Some examples of Schedule III drugs are: products containing less than 90 milligrams of codeine per dosage unit (Tylenol with codeine), ketamine, anabolic steroids, and testosterone.

Schedule IV

Schedule IV drugs, substances, or chemicals are defined as drugs with a low potential for abuse and low risk of dependence. Some examples of Schedule IV drugs are: Xanax, Soma, Darvon, Darvocet, Valium, Ativan, Talwin, Ambien, and Tramadol.

Schedule V

Schedule V drugs, substances, or chemicals are defined as drugs with lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of certain narcotics. Schedule V drugs are generally used for antidiarrheal, antitussive, and analgesic purposes. Some examples of Schedule V drugs are: cough preparations with less than 200 milligrams of codeine or per 100 milliliters (Robitussin AC), Lomotil, Motofen, Lyrica, and Parepectolin.

EARLY PHASE PRECLINICAL AND CLINICAL STUDY – DATA REVIEW

The early phase preclinical and clinical study data is collectively reviewed by several agencies to determine drug scheduling. Some of the key information considered includes data from:

1. Chemistry studies
2. Receptor-ligand binding studies and functional (second messenger) studies
3. Pharmacokinetic studies in animals and humans
4. Abuse-related studies in animals:
    a. General behavioral observations from safety pharmacology studies
    b. Drug discrimination study
    c. Self-administration study
    d. Physical dependence study
5. Abuse-related studies in humans:
    a. Human abuse potential study
    b. Physical dependence study
6. Abuse-related adverse events (AEs) from clinical studies
7. Information related to overdose, both intentional and accidental, during clinical studies
8. Assessment of the incidence of abuse during clinical studies

Beginning with first-in-human trials, all drugs (including non-CNS) should be evaluated for CNS AEs, including but not limited to: euphoria, somnolence, agitation, and dizziness. Conducting early CNS testing is helpful because early trials include higher doses, which allows for better characterization of pharmacology.

Subjective evaluations allow for correlations between subjective and objective impairment, as more intense PK sampling takes place in the early phases of research. All this data is important safety information for later phase patient trials.

If early testing indicates no impairing effects, this information can be used to secure waivers for future requirements, which helps accelerate the development of your drug.

However, if early analysis indicates there are potential impairing effects, a development program should include pharmacokinetic assessments during Phase II/III. Factors affecting exposure should be documented (e.g., food, time of dosing, and concomitant medications), and there should be monitoring conducted at specified intervals for temporal impairment risk. Additional data should focus on open-ended and targeted AE collection, such as reports of motor vehicle accidents (MVA) and traffic violations. Additionally, it is helpful to monitor for effects that might not have been previously identified (e.g., impaired executive function and memory).

Some significant considerations for CNS drug development include:

Abuse Potential

The decision to undertake additional preclinical and clinical testing to evaluate human abuse potential (HAP) will largely depend on the preclinical and clinical data already collected and reviewed at the End-of-Phase II meeting with the FDA. Relevant adverse events, target receptors, and other signals of abuse potential are carefully examined by regulators to determine if there may be a need for further data and consideration of scheduling status. Understanding this early in development assures preparedness for your program's budget and timeline.

HAP studies evaluate 'likeability' of a drug in a face-valid population. Typically, they are single-dose, double-blind crossover studies in non-dependent recreational drug users, comparing an investigational drug to both placebo and active controls. Scheduled controls can include opioids, stimulants, depressants, sedative/hypnotics, cannabinoids, and/or hallucinogens. The study will encompass:

- Pharmacological challenge to ensure non-dependence and sensitivity to active control
- Subjective/objective measures to evaluate drug effects, cognition, and motor skills
- Computerized testing administered on tablets

Formulations evaluating abuse-deterrent properties will also include HAP studies on the formulation's effectiveness in mitigating abuse by different routes of administration. Preclinical models usually precede HAP studies and include animal models of self-administration, drug discrimination, and conditioned place preference.

Physical Dependency/Withdrawal

Distinct from, but related to, abuse potential, is the possibility of physical dependency; that is withdrawal symptoms that occur when the drug is suddenly stopped or drastically reduced. The question of physical dependency is addressed in the FDA guidance titled Assessment of Abuse Potential of Drugs. It requires thorough preclinical and clinical evaluation in order to properly inform drug schedule decisions and provide relevant safety information in section 9.3 of the product label.

Withdrawal definition:
A state of adaptation that is manifested by a drug class – specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, reducing blood level of the drug, and/or administration of an antagonist.

Preclinical study includes assessment of withdrawal in animals. These are typically related to physiological and behavioral assessments and are limited to the scope of withdrawal symptoms that may occur in humans.

Clinical analysis in human subjects is usually conducted in Phase II/III trials, after study drug termination. These assessments need to be carefully planned and included in the study design, as prescheduled assessments/visits are required during the discontinuation period. When abrupt drug discontinuation may be contraindicated in a patient population, a dedicated physical dependency (withdrawal) study may be needed in healthy normal volunteers. There are different approaches you can take, depending on the type of evaluation needed and the measures best suited for your investigational drug.

Some of the relevant parameters of the placebo-controlled dependency study include:

- Minimum 30-day exposure followed by observed withdrawal period (dependent on half-life)
- Assessment of adverse events and validated drug withdrawal questionnaires
- Assessment of rebound effects (patient population)

A number of validated tools are available for the assessment of withdrawal symptoms for various classes of drugs, including but not limited to the ones described below.

Opiates withdrawal scales

- Clinical Opiate Withdrawal Scale (COWS)
- Subjective Opiate Withdrawal Scale (SOWS)

Benzodiazepines withdrawal scales:

- Physicians Withdrawal Checklist (PWC-20 and PWC-34)
- Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ)
- Clinical Institute Withdrawal Assessment - Benzodiazepines (CIAW-B)

Stimulants withdrawal scales:

- Amphetamine Withdrawal Questionnaire (AWQ)
- Cocaine Selective Severity Assessment (CSSA)

Cannabinoids withdrawal scale:

- Cannabis Withdrawal Scale (CWS)
- Marijuana Withdrawal Checklist (MWC)

SSRI withdrawal scale

Discontinuation Emergent Signs and Symptoms Checklist (DESS)

Driving Impairment Assessment — Cognitive and Motor Function Effects

CNS-active drugs, by their nature, may affect cognitive abilities and motor function. A key parameter that has been specifically identified by the FDA as warranting study is impact on driving ability while under the effect of the drug, or the morning after. Driving simulation studies require specialized equipment and highly trained experts. If a drug shows effects on psychomotor function, a dedicated driving study may be required to fully evaluate the ability of an exposed patient to operate a motor vehicle (refer to guidance).

The FDA has endorsed a tiered approach to the assessment of drug-impaired driving. Tiered development includes a Standardized Behavioral Assessment early in drug development, consisting of pharmacology/toxicology, epidemiology, and clinical/standardized behavioral assessments. Tests used early in drug development should have high sensitivity for impairment. Later in development, studies should clarify the clinical relevance of these earlier findings.

Functional domains of importance for driving assessment include:

- Alertness/arousal/wakefulness
- Attention and processing speed
- Reaction time/psychomotor functions
- Sensory-perceptual functioning
- Executive functions

Driving studies can be conducted with validated driving simulators or on-the-road testing. Simulators enable a stricter control of driving conditions, involves less risk of injury to participants, and are more cost-effective than on-road testing. In such studies, subjects are evaluated for driving ability before and after drug exposure, and designs can include both positive and placebo controls. Driving studies are customized for the specific drug under investigation. For example, testing for somnolence or low attention will require a different test than one that looks for aggressiveness or increased risk-taking. Other methodological considerations include enrolling the appropriate participants (those that are part of the target market for the drug); evaluating both initial and chronic drug exposure; and testing at the highest exposures likely to be encountered during clinical use. It is important to determine the time-course of exposure and any tolerance that may develop.

Evaluation of CNS effects may also include cognitive or psychomotor enhancements of drugs. Some of the parameters include:

- Attention
- Memory
- Visual perceptual functions
- Sequencing functions
- Logical problem solving
- Psychomotor speed and coordination
- Simultaneous information processing abilities
- Executive functions

Additive Effects

For CNS-active compounds, it is particularly important to understand the impacts of the drug when combined with other medications, marijuana and other recreational drugs, or alcohol. Conducting the appropriate evaluations of the additive or complementary effects of such substances is essential. Determining the risk for both CNS-impairing effects as well as physiological effects (e.g., increased respiratory depression) is critical in understanding the potential safety implications of drug-drug and drug-alcohol interactions.

Suicidality and ideation are also typically assessed during clinical development with validated scales such as the Columbia-Suicide Severity Rating Scale (C-SSRS), to determine any impact on suicidal ideation or attempts.

CHOOSING A CRO FOR CNS STUDIES

When sponsors make the decision to invest resources into a comprehensive analysis of the critical CNS-specific questions at the outset, the path forward for a drug has fewer unknowns. Having already studied the salient issues, you can be more confident in the trials that will be required to complete the pathway to market, and you will have the opportunity to fully understand the future budget and timeline implications. Determining if your drug is at less risk for critical safety factors, such as abuse potential or impairing effects, can provide important information to leverage regulatory review status and/or funding and investment opportunities. Understanding your program early in development and creating a robust strategy for regulatory development enables better accuracy in predicting timelines and budgetary needs for your programs.

Partnering with a CRO that has relevant, current, and extensive experience in the analysis of these additional considerations for a CNS-active agent is crucial. Altasciences is that CRO.

Altasciences is the only North-American CRO with 10 permanently installed driving simulators on-site. Our experts can also recommend surrogate measures of motor function and cognition that can help determine early on if further testing will be required (or waived) for your program. We have the leading expertise on human abuse and physical dependency evaluation, and our key opinion leaders can help you strategically implement a comprehensive regulatory and drug development pathway.

We have controlled substance licenses and secure, configurable, locked facilities that can accommodate any type of abuse potential trial.

Altasciences is truly a center of excellence when it comes to comprehensive, complex, multi-faceted CNS drug evaluations. See our relevant expertise here:

Case Studies

Evaluating the Abuse Potential of Mirogabalin

Achieving a 505(b)(2) Regulatory Approval, Multiple NDA-enabling Studies Including Driving

The Altascientist (previous issues)

Issue No. 3. Assessing Human Abuse Potential to Limit the Misuse and Abuse of Prescription Drugs

Issue No. 1. Studying the Effects of Drugs on Driving

Webinars

Strategic Considerations for a Successful CNS Development Pathway

Amphetamine to Zolpidem, Navigating the ABCs of Early Phase CNS Drug and Cannabinoid Development

Cracking the Pill: A Journey of Exploring Abuse-Deterrent Methods from the Laboratory to the Real User. Includes a candid interview with recreational drug users

See the rest of our webinars on a variety of topics.

Driving simulation expertise including video

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, and data management, all customizable to specific sponsor requirements.

Altasciences helps sponsors get better drugs to the people who need them, faster.