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Identifying Appropriate Outcome Measures and Methodology to Evaluate the Abuse, Misuse, Dependence, and Impairing Effects of CNS-Active Drugs in Healthy Volunteer and Patient Trials

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Abstract

Introduction: Characterizing the pharmacological profile of a CNS-active drug, including abuse/dependence potential and impairing effects, is an important component of establishing the safety and risk profile. Such an evaluation is based on a composite of various data, including *in vitro*, preclinical, clinical, and any available post-marketing data.

Methods: A review of regulatory guidances, literature, and unpublished data to provide examples of strategies for evaluating CNS drug risk evaluation.

Results: Studies such as human abuse potential and driving simulation are often required to provide surrogate data for risk identification. However, all preclinical and clinical data is reviewed for risks. Several strategies to obtain data related to aberrant drug behaviors (i.e., abuse, misuse and/or diversion) can be considered. This includes monitoring key adverse events, urine drug testing, risk assessment questionnaires, drug accountability, and noncompliance, amongst other measures. Cognitive impairment may also be assessed throughout a clinical program. New tools are emerging to specifically probe on such events in the patient population, particularly because most events related to abuse, misuse, diversion, overdose, dependence, and addiction will likely require further evaluation and interpretation. Examination of aberrant behaviors would benefit from a structured method to collect information that may aid in understanding whether a specific behavior or adverse event is related to abuse or misuse.

Conclusions: Specific adverse events and questionnaires may be utilized to evaluate drug withdrawal and dependence, and contribute to the abuse potential evaluation of a drug's safety profile. The available methods and limitations are reviewed.

Introduction

CNS-active drugs have pharmacological attributes that require specific evaluation during drug development:

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

Cognitive Impairing/Enhancing Effects

Tests of cognition: Evaluation of CNS effects may include cognitive or psychomotor enhancements of drugs assessed early in the development program where larger ranges of doses are studied.

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

Impairing effects are relevant for patient safety. These may also be studied in conditions when a drug is co-administered with other drugs or alcohol to determine if there is a resulting additive effect.

Driving Simulation

The FDA identified drug-impaired driving as a public health priority:[1]

- Systematic effort to identify drugs that increase the risk of motor vehicle accidents (MVA) and reduce that risk
- Patient self-perception is not adequate for evaluating the presence or degree of driving impairment.

Objective information about how a drug affects driving may be needed to enable safe use. **Drugs that require evaluation for driving impairment include:**

- Drugs intended for chronic (including chronic-intermittent) outpatient use by adults who drive
- Psychoactive and non-psychoactive drugs e.g., impaired consciousness from hypoglycemic reaction to a glucose lowering drug, impaired vision from a mydriatic drug
- Drugs that have the potential to improve driving performance by decreasing somnolence, but might increase risk-taking e.g., stimulants, aggressive driving
- Drugs intended to be taken at night (residual daytime effects)

Functional domains of importance include:

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

Figure 1. Driving simulator cockpit CRCDS-MiniSim® for drug evaluation.

DRUG	Time Post-Dose	SDLP (cm) vs Placebo, (95% CI)
Flibanserin 100 mg (5)	8.0 hours	-2.47 (-3.9, -1.0)
Flibanserin 200 mg (5)	8.0 hours	-1.40 (-2.8, 0.0)
Tolperisone 450 mg (3)	3.0 hours	0.20 (-3.0, 3.4)
Gabapentin 250mg (4)	7.25 hours	0.55
Diphenhydramine Citrate 76mg (4)	7.25 hours	2.37 (1.0, 4.0)
Zopiclone 7.5mg (2)	8.0 hours	3.50 (2.5, 4.9)
ETOH .05 BAC (6)	N/A	4.40
ETOH .08 BAC (6)	N/A	5.80
Diphenhydramine Hall 50 mg (4)	3.0 hours	6.19 (4.8, 7.6)
ETOH .10 BAC (6)	N/A	7.90
Cyclobenzaprine 30 mg (3)	3.0 hours	8.80 (5.6, 12.0)
Triazolam 0.5mg (4)	7.25 hours	13.82 (10.9,17.4)
Alprazolam 1mg (7)	1.5 hours	22.71 (20.2,25.2)

Table 1. Summary of Standard Deviation of Lateral Position (SDLP) change from placebo (results from six independent studies).[2]

Abuse Potential Evaluation

Assessment of abuse potential is required for FDA and Health Canada submissions to determine drug scheduling (Controlled Substances Act).[3]

Evaluation of the likelihood that a drug may be abused once marketed is required if a drug:

- Affects the central nervous system (CNS)
- Is chemically or pharmacologically similar to other drugs with known abuse potential
- Produces psychoactive effects e.g., sedation, euphoria, mood changes
- Is formulated with abuse-deterrent properties

Evaluates subjective drug effects in a face-valid population:

- Single-dose, double-blind crossover studies
- Non-dependent recreational drug users
- Placebo- and active-controlled
- Scheduled controls e.g., opioids, stimulants, depressants, sedative/hypnotics, cannabinoids, and/or hallucinogens
- Pharmacological challenge to ensure non-dependence and sensitivity to active control
- Limitations in sample size (24-60 subjects)

Study Endpoints:

- Subjective measures include visual analog scales for drug liking, high, good drug effects, bad drug effects, any drug effects, overall drug liking, take drug again
- Addiction Center Research Inventory (ARCI) and measures of pharmacological effects (e.g., Bowdle VAS, sedation, hallucinations)
- Cognitive measures to evaluate impairing effects (psychomotor processing speed, attention, balance)

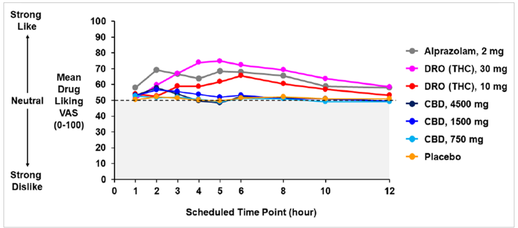

Figure 2. Drug liking VAS scores for cannabidiol (CBD), dronabinol (DRO), alprazolam, and placebo, over time.[4]

Abuse, Misuse, Overdose, and Physical Dependence

Adverse events and incidences of aberrant behaviors are important in determining risk of abuse, misuse, and overdose.[3]

Adverse events of interest include:

- Euphoria-related terms: euphoric mood; elevated mood; feeling abnormal; feeling drunk; feeling of relaxation; dizziness; thinking abnormal; hallucination; inappropriate affect
- Terms indicative of impaired attention, cognition and mood, somnolence, mood disorders and disturbances
- Dissociative/psychotic terms: psychosis, aggression, confusion and disorientation
- Related terms not captured elsewhere: drug tolerance, habituation, drug withdrawal syndrome, substance-related disorders

Endpoints related to aberrant drug behaviors:

- Abnormal urine drug screen
- Repeat refill requests/aberrant drug accountability/missing medication
- Overdose/medication error (intentional vs. unintentional)
- Interpretation requires additional information captured in narrative (circumstances, adverse events, etc.)

Aberrant drug assessment tools:

- MADDERS: Misuse, abuse, and diversion drug event reporting system[5]
- Self-reported: Misuse, Abuse, and Diversion (SR-MAD) questionnaire [6]

Physical dependence /drug withdrawal assessed with adverse events and questionnaires following abrupt drug discontinuation following chronic (>30 day) drug exposure.

Physical dependence (drug withdrawal scales)

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 scales:

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

SSRI withdrawal scale:

- Discontinuation Emergent Signs and Symptoms Checklist (DESS)

Conclusions

- CNS drug development requires additional considerations to assess risk and safety.
- Cognitive impairing and enhancing effects can influence risk on activities, such as driving or use of heavy machinery.
- CNS drugs may need to be evaluated for their abuse and physical dependence potential to determine if a drug needs to be scheduled at the time of approval.
- Various questionnaires and tests should be included throughout the clinical development program to evaluate CNS drugs.

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