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Development of the Subject-Rated Comprehensive Drug Withdrawal Scale (CDWS) to Evaluate the Physical Dependence Potential of Investigational Drugs

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ABSTRACT

AIM: To develop a comprehensive, subject-rated scale that can be frequently administered in a clinical investigational drug trial to evaluate potential signs and symptoms of physical dependence and withdrawal. Novel drugs with abuse potential are assessed for physical dependency as part of the approval process under the Controlled Substances Act. Several drug class-specific withdrawal scales are available; however, these are mostly clinician-rated, challenging to administer frequently in late-stage clinical trials, and contain questions irrelevant to non-drug-abusing populations.

METHODS: A review of the published literature and scales of withdrawal were evaluated for the presentation of symptoms and intensity ratings related to drug withdrawal syndrome resulting from various classes of drugs. A collective list of symptoms was identified, and each term was evaluated for comprehension and ease of administration using SMOG and Flesch Kincaid Readability scoring. Questions were drafted to include comprehensive language and past tense suitable to evaluate symptoms (current and past 24 hours). Validation of the scale for content, comprehension, and appropriateness of the recall period is ongoing.

RESULTS: Following a thorough literature review, 62 drug withdrawal symptoms associated with scheduled and unscheduled drug classes were identified. A standard Likert 0–3-point rating scale was selected where 0 = no symptoms and 1-3 range from mild, moderate to severe, respectively. The SMOG Readability measures ensure comprehension at no greater than a 6th-grade reading level (easy to read). The Flesch Kincaid Readability scoring identified some terms (e.g., diarrhea, constipation) deemed more than a grade 8 level. Validity testing is ongoing, and results will be presented.

CONCLUSION: A reliable subject-reported withdrawal scale is needed to effectively evaluate potential signs and symptoms of drug discontinuation in clinical trials evaluating new drugs in development. A novel CDWS tool is currently being developed to address existing scales' pragmatic and validity concerns.

INTRODUCTION

Physical dependence is a physiological adaptation associated with the chronic administration of a drug. Abrupt discontinuation reduced systemic exposure, or administration of a drug antagonist can produce withdrawal symptoms ranging from benign to life-threatening.[1]

The evaluation of physical dependence is an important consideration in the scheduling of drugs under the Controlled Substances Act.

The evaluation of physical dependence of investigational drugs is typically addressed in the target patient population during phase III clinical trials.

Existing withdrawal scales and questionnaires present several limitations:

- Most scales are clinician-rated, rendering frequent assessments impractical (**Table 1**).
- Most scales were validated in drug-abusing populations and may contain questions not directly relevant to patient populations (e.g., craving).
- Most withdrawal scales are drug-class specific and may not cover symptoms related to novel drugs or drugs with novel mechanisms of action.

OBJECTIVE

To develop a comprehensive subject-rated scale well-suited for a frequent evaluation of potential signs and symptoms of physical dependence and withdrawal both in clinical practice and during clinical investigational drug trials.

METHODS

A review of the published literature identified existing validated scales of drug withdrawal (**Table 1**) along with published reviews of signs and symptoms of drug withdrawal. Signs and symptoms of withdrawal described in the Diagnostics and Statistical Manual – Version 5 (DSM-5) were also reviewed. A list of relevant terms was compiled for all drug classes known to produce physical dependence including[1]:

Scheduled drug classes: opiates/opioids, benzodiazepines, barbiturates, gabapentin, ketamine, cannabinoids/cannabis, Z-drugs (zolpidem, zaleplon and eszopiclone), stimulants, and testosterone/androgenic anabolic steroids.

Unscheduled drug classes: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase inhibitors, alcohol, anti-parkinsonian drugs, antipsychotics, aspirin, nicotine/tobacco, statins, and corticosteroids.

Each sign and symptom was reviewed to check if it could be asked directly. Symptoms requiring a clinician to evaluate (including symptoms specific to neonatal withdrawal) or devices to measure were omitted. Symptoms repeated across scales were consolidated to avoid repetition. Symptoms capturing acute and protracted withdrawal were included.

The questionnaire was developed for an english-speaking population and structured to be answered using a 4-point Likert rating scale with symptoms rated according to their absence (0) or increased severity ranging from 1 to 3 (mild, moderate, and severe), similar to adverse event grading. Questions were worded to enable daily or more frequent administration. The SMOG Readability and Flesch Kincaid Readability literacy tools were used to achieve a grade 8 or below reading level for the instructions and individual items.

Table 1. Existing self- or clinician-rated scales and questionnaires evaluating drug class-specific withdrawal symptoms.

Drug Class	Scale	Self-rated? Y/N
Opiates	Clinical Opiate Withdrawal Scale (COWS)[2]	N
	Subjective Opiate Withdrawal Scale (SOWS)[3]	Y
	Objective Opiate Withdrawal Scale (OOWS)[3]	N
	Clinical Institute Narcotic Assessment (CINA)[4]	N
Benzodiazepines	Penn Physician Withdrawal Checklist (PWC-20 and PWC-34)[5,6]	N
	Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ)[7]	N
	Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B)[8]	N
	Benzodiazepine Dependence Questionnaire (BDEPQ)[9]	Y
Stimulants	Amphetamine Withdrawal Questionnaire (AWQ)[10]	N
	Cocaine Selective Severity Assessment (CSSA)[11]	N
	Caffeine Withdrawal Symptom Questionnaire[12]	Y
Cannabinoids	Cannabis Withdrawal Scale (CWS) [13]	Y
	Marijuana Withdrawal Checklist (MWC)[14]	N
SSRIs*	Discontinuation Emergent Signs and Symptoms Checklist (DESS)[15]	N
Alcohol	Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)[16]	N
Pediatric Opioids and Benzodiazepines	Sophia Observation Withdrawal Symptoms (SOS)[17]	N
	Withdrawal Assessment Tool-1 (WAT-1)[18]	N

*SSRIs = Selective Serotonin Reuptake Inhibitors

Table 2. Drug withdrawal symptoms according to disorder type expressed in medical terminology.

Category	Symptoms	
Psychiatric Disorders	Anxiety	Depersonalization
	Irritable	Derealization
	Detached	Perceptual changes
	Paranoia	Aggression (non-directed)
	Visual hallucination	Aggression (self/others)
	Auditory hallucination	
Mood and Cognitive Disorders	Thoughts racing	Dysphoric mood
	Difficulty concentrating	Memory impaired
	Difficulty expressing thoughts	Speech impaired
	Depressed mood	Anhedonia/uncontrolled crying
	Confusion/disoriented	Mood swings
Nervous System Disorders	Dizziness	Electric shock sensations
	Lightheadedness	Distorted smell/taste
	Tremor	Impaired gait
	Headache	Uncontrolled movement tongue/mouth
	Weakness	Syncope
	Tingling/numbness	Loss of consciousness
	Seizures	
Sleep Disorders	Alert	Yawning
	Somnolence	Fatigue
	Restless	Insomnia
	Agitation	Nightmares
Gastrointestinal Disorders	Constipation	Vomiting
	Diarrhea	Appetite loss
	Abdominal cramps	Dry mouth
	Nausea	Hypersalivation
Musculoskeletal Disorders	Muscle/bone ache	Muscle cramp
	Muscle twitch	Stiffness
Cardiovascular Disorders	Hot flash	Palpitations
	Hyperventilation	
Eye and Ear Disorders	Lacrimation	Eyes sore
	Vision blurred	Tinnitus
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	Piloerection
General and Other Disorders	Chills	Runny nose

RESULTS

A total of 62 unique drug withdrawal symptoms that could be reasonably self-reported were identified. Terms requiring diagnostic instrumentation, laboratory testing, or clinician observations were omitted (for example, changes in pupil diameter, heart rate, blood pressure, respiratory rate, arterial oxygen saturation, low-density lipoproteins [LDL], hyponatremia, hyperkalemia, ventricular tachycardia, arrhythmia, and other clinical laboratory outcomes).

The application of the SMOG Readability measure found that all questionnaire terms required a reading level no greater than grade 6 (easy to read). Reducing the character/word count for instructions and individual items further improved readability. The second application of the SMOG Readability measure confirmed all the individual items' scores to equal 3.13 (grade 5 or lower – very easy to read) or 8.84 (grade 6). The revised questionnaire was then evaluated using the Flesch Kincaid Readability, which found scores for instructions and most individual items to range from grade 5 (very easy to read) to grade 8/9 (plain english). Some terms (i.e., diarrhea, constipation, difficulties speaking, mouth or tongue moving uncontrollably, trouble concentrating, disoriented or confused) were identified as corresponding to a college grade level (difficult to read). Other terms (i.e., irritable, goosebumps, breathing faster than usual) were identified as corresponding to a college grade level (difficult to read), and some terms (i.e., irritable, goosebumps, breathing faster than usual) were identified as corresponding to a grade 10-12 level (fairly difficult to read). These terms were individually reviewed, and the wording was simplified. Questions were adjusted to allow for daily or more frequent evaluations. Symptoms were organized into major categories, as indicated in **Table 2**. A scoring and interpretation algorithm is currently under development.

DISCUSSION

Current withdrawal scales are mostly clinician-administered and impose limitations on the clinical trial evaluation of physical dependency on novel investigational drugs or monitoring therapeutic efficacy in real-world situations. Safe management of patients relies on understanding the risk of physical dependency, and thus, this is an important factor in drug scheduling under the Controlled Substance Act. The Comprehensive Drug Withdrawal Scale (CDWS) is a self-reported questionnaire intended to evaluate possible signs and symptoms associated with investigational or marketed drugs in clinical and research environments. The CDWS can be administered prior to and after the abrupt discontinuation or tapering of a chronically administered drug (≥ 28 days) to monitor for acute and protracted withdrawal. Based on an extensive review of existing withdrawal measures, 62 non-overlapping, directly noticeable symptoms were identified. Readability tools were deployed to expand ease of administration to a wide range of patients. The CDWS was developed to help characterize the nature and intensity of symptoms associated with drug discontinuation and not as a diagnostic aid.

The CDWS is intended to add value to the available modalities for evaluating withdrawal symptoms in clinical trials. An algorithm is also being developed to assist in the identification of potential patterns or clusters of withdrawal symptoms that may be specific to a drug or class of drugs.

CONCLUSIONS

A reliable subject-reported withdrawal scale is needed to effectively evaluate potential signs and symptoms of drug discontinuation in clinical trials evaluating new drugs under development. A novel CDWS tool is currently being developed to address the pragmatic and validity concerns of existing scales.

Disclosures: The viewpoints expressed are those of the authors and not their respective employers.

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