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

Beatrice Setnik^{1,2}, Denise Milovan¹

¹Altasciences, QC, Canada; ² University of Toronto, Department of Pharmacology and Toxicology, ON, Canada

ABSTRACT

METHODOLOGICAL ISSUE BEING ADDRESSED: Novel drugs with abuse potential are assessed for physical dependency as part of the approval process under the Controlled Substances Act. While several withdrawal scales exist, these tend to be drug-specific, clinician-rated, and challenging to administer frequently during latestage clinical trials. Additionally, many scales contain items irrelevant to non-drug-abusing populations. A new, comprehensive, self-reported scale that covers a broad spectrum of common withdrawal symptoms is under development and is designed to be easily and frequently administered in clinical trials to assess potential physical dependence and withdrawal signs.

INTRODUCTION: Physical dependence evaluation requires monitoring of signs and symptoms of acute and protracted withdrawal during a period following abrupt drug discontinuation. Most assessments are conducted following drug discontinuation in Phase II or III patient trials, but clinic visits limit continuous monitoring. Thus, innovative methods are needed to gather safety data throughout the withdrawal period, ideally through selfadministered daily reports. The limitations of existing withdrawal scales highlight the need for broader, more versatile measures that can be self-administered across various drug classes and patient populations.

METHODS: A literature review was conducted to identify withdrawal symptoms and intensity ratings associated with various drug classes. A comprehensive list of symptoms was compiled, eliminating redundancies and focusing on those suitable for self-administration. A 0–3 Likert scale (0 = no symptoms, 1–3 = mild to severe) was selected to assess symptom severity. To ensure accessibility, readability was evaluated using the SMOG and Flesch-Kincaid readability tests. Questions were phrased appropriately for self-reporting symptoms over the past 24 hours. Validation of content, comprehension, and recall period is ongoing.

RESULTS: The literature review identified 62 distinct withdrawal symptoms that could be self-administered and are relevant across both scheduled and unscheduled drug classes. Symptoms requiring clinical equipment (e.g., blood pressure measurement and pupillometry) were excluded. The SMOG index confirmed that all items were comprehensible at or below a 6th-grade reading level. At the same time, Flesch-Kincaid readability scores suggested that certain terms (e.g., "diarrhea," "constipation") may require simplification for lower reading levels. Validation is ongoing, and the full set of 62 items will serve as a symptom bank, from which subscales can be tailored to match the adverse event profile of specific drugs.

CONCLUSION: A reliable, self-reported withdrawal scale is critical for evaluating withdrawal symptoms during drug discontinuation in clinical trials of new drugs. The development of the novel Clinical Drug Withdrawal Scale (CDWS) addresses the limitations of existing scales, aiming to provide a valid, easy-to-use tool that can be widely applied across diverse patient populations and drug types.

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-threatening¹.

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 patien 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.



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	Υ
	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	Υ
Stimulants	Amphetamine Withdrawal Questionnaire (AWQ) ¹⁰	N
	Cocaine Selective Severity Assessment (CSSA) ¹¹	N
	Caffeine Withdrawal Symptom Questionnaire ¹²	Υ
Cannabinoids	Cannabis Withdrawal Scale (CWS) 13	Υ
	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	Sophia Observation Withdrawal Symptoms (SOS) ¹⁷	N
Opioids and Benzodiazepines	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		
	Anxiety	Depersonalization	
	Irritable	Derealization	
Developed to Discondance	Detached	Perceptual changes	
Psychiatric Disorders	Paranoia	Aggression (non-directed)	
	Visual hallucination	Aggression (self/others)	
	Auditory hallucination		
	Thoughts racing	Dysphoric mood	
	Difficulty concentrating	Memory impaired	
Mood and Cognitive Disorders	Difficulty expressing thoughts	Speech impaired	
	Depressed mood	Anhedonia/uncontrolled crying	
	Confusion/disoriented	Mood swings	
	Dizziness	Electric shock sensations	
	Lightheadedness	Distorted smell/taste	
	Tremor	Impaired gait	
Nervous System Disorders	Headache	Uncontrolled movement tongue/mouth	
	Weakness	Syncope	
	Tingling/numbness	Loss of consciousness	
	Seizures		
	Alert	Yawning	
Olana Diagrafara	Somnolence	Fatigue	
Sleep Disorders	Restless	Insomnia	
	Agitation	Nightmares	
	Constipation	Vomiting	
O('((' D'	Diarrhea	Appetite loss	
Gastrointestinal Disorders	Abdominal cramps	Dry mouth	
	Nausea	Hypersalivation	
M	Muscle/bone ache	Muscle cramp	
Musculoskeletal Disorders	Muscle twitch	Stiffness	
Dandierra anden Die enden	Hot flash	Palpitations	
Cardiovascular Disorders	Hyperventilation		
	Lacrimation	Eyes sore	
Eye and Ear Disorders	Vision blurred	Tinnitus	
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	Piloerection	
General and Other Disorders	Chills	Runny nose	

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-TR (DSM-5-TR) were also reviewed. A list of relevant terms was compiled for all drug classes known to produce physical dependence including¹:

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's evaluation (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.

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) correspond 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 nonoverlapping, 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 concerns about the pragmatic and validity of existing scales.

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