

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 late-stage 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 self-administered 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 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.

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

REFERENCES

1. Lerner A, Klein M. Dependence, withdrawal and rebound of CNS drugs: an update and regulatory considerations for new drugs development. *Brain Commun.* 2019 Oct 16;1(1):fcz025.
2. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs.* 2003 Apr-Jun;35(2):253-9.
3. Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse.* 1987;13(3):293-308.
4. Peachey JE, Lei H. Assessment of opioid dependence with naloxone. *Br J Addict.* 1988;83:193–201.
5. Rickels K, Schweizer E, Case WG, et al. Long-term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation. *Arch Gen Psychiatry.*1990;47:899-907.
6. Rickels K, Garcia-Espana F, Mandos LA, Case GW. Physician Withdrawal Checklist (PWC-20). *J Clin Psychopharmacol.* 2008 Aug;28(4):447-51.
7. Tyrer P, Murphy S and Riley P (1990) The Benzodiazepine withdrawal symptom questionnaire. *J. Affective Disorders* 19: 53-61.
8. Busto UE, Sykora K, Sellers EM. A clinical scale to assess benzodiazepine withdrawal. *J Clin Psychopharmacol.* 1989 Dec;9(6):412-6.
9. Baillie AJ, Mattick RP. The benzodiazepine dependence questionnaire: development, reliability and validity. *Br J Psychiatry.* 1996 Sep;169(3):276-81.
10. Sisurapanont M, Jarusuraisin N, Jititwutikan J. Amphetamine withdrawal: I. Reliability, validity and factor structure of a measure. *Aust N Z J Psychiatry.* 1999 Feb;33(1):89-93.
11. Kampman KM, Volpicelli JR, McGinnis DE, Alterman AI, Weinrieb RM, D'Angelo L, Epperson LE. Reliability and validity of the Cocaine Selective Severity Assessment. *Addict Behav.* 1998 Jul-Aug;23(4):449-61.
12. Juliano LM, Huntley ED, Harrell PT, Westerman AT. Development of the caffeine withdrawal symptom questionnaire: caffeine withdrawal symptoms cluster into 7 factors. *Drug Alcohol Depend.* 2012 Aug 1;124(3):229-34.
13. Allsop DJ, Norberg MM, Copeland J, Fu S, Budney AJ. The Cannabis Withdrawal Scale development: patterns and predictors of cannabis withdrawal and distress. *Drug Alcohol Depend.* 2011 Dec 1;119(1-2):123-9.
14. Budney AJ, Novy PL, Hughes JR. Marijuana withdrawal among adults seeking treatment for marijuana dependence. *Addiction.* 1999. 94(9). 1311-1322.
15. Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome: A randomized clinical trial. *Biol Psychiatry* 1998; 44: 77–87.
16. Sullivan, J.T.; Sykora, K.; Schneiderman, J.; Naranjo, C.A.; and Sellers, E.M. Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). *British Journal of Addiction* 84:1353-1357, 1989.
17. Ista E, van Dijk M, de Hoog M, Tilboel D, Duivenvoorden HJ. Construction of the Sophia Observation withdrawal Symptoms-scale (SOS) for critically ill children. *Intensive Care Med.* 2009 Jun;35(6):1075-81.
18. Franck LS, Harris SK, Soetenga DJ, Amling JK, Curley MA. The Withdrawal Assessment Tool-1 (WAT-1): an assessment instrument for monitoring opioid and benzodiazepine withdrawal symptoms in pediatric patients. *Pediatr Crit Care Med.* 2008 Nov;9(6):573-80.

Scan the QR code to access the poster presentation

