Practical Considerations for the Evaluation of Physical Dependence and Drug Withdrawal for Novel CNS-Active Drugs in Clinical Trials

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ABSTRACT

INTRODUCTION: Chronic exposure (over 4 weeks) to certain drugs can lead to physical dependence (PD) and withdrawal symptoms (WS), which can be severe. The FDA's 2017 guidance on the Assessment of Abuse Potential of Drugs recommends evaluating PD following the abrupt discontinuation of novel CNS-active compounds. However, current PD evaluations during Phase III patient trials face challenges due to patient non-compliance with frequent administration of drug-class-specific withdrawal scales, disease-specific scales, adverse event (AE) monitoring, measuring physiological and pharmacodynamic effects, and collecting blood samples for pharmacokinetic (PK) analysis. Many of the relevant scales are clinician-rated and are not validated for patients without substance use disorders. Additionally, many assessments cannot be self-administered (eg, cardiac or brain activity measurements) and require in-person clinic visits, limiting the frequency of data collection. When PD is identified, guidance for effective drug tapering or conversion schemes is often lacking, highlighting the need to assess PD earlier in drug development. Current study designs must be adapted to better capture withdrawal symptoms throughout the relevant timeframe.

METHODS: A working group of industry leaders with clinical trial experience met monthly from February to December 2024 to review FDA requirements, identify existing methodological limitations, and propose new, pragmatic methods to address clinical trials objectives. The group identified key challenges and recommended adaptations to existing trial designs and data collection methods.

RESULTS: The working group recommends several pragmatic methods to evaluate PD. A subject-rated withdrawal scale, the Comprehensive Drug Withdrawal Scale, is being developed for frequent use in clinical trials involving both patient and healthy populations. This tool would be administered via a daily diary, similar to how AEs and concomitant medications are tracked. Disease-specific scales and subjective measures of WS and mood states may also be adapted for repeated, clinician-assisted or self-reported, virtual evaluations. Telemedicine and wearable devices approved by regulatory agencies could enable remote collection of physiological data and reduce the need for frequent in-clinic visits. Advances in PK assays, which require large blood volumes (up to 10 mL), may soon allow for remote collection via microsampling (10-20 µL). Evaluating WS in early-phase trials with healthy volunteers may help minimize late-phase confounders such as use of concomitant medications, provide insights into rebound effects, and assist in developing tapering or conversion protocols for later patient studies. Emerging artificial intelligence (AI) technologies may further enhance the prediction and interpretation of PD safety signals.

CONCLUSION: PD and WS following chronic drug exposure are critical safety concerns that must be addressed during drug development. However, evaluating these requires trial designs that support frequent symptom assessments following abrupt drug discontinuation. The working group has identified several key adaptations that can be incorporated into clinical trials to facilitate frequent collection of PD and withdrawal symptoms. The integration of new instruments, telemedicine, wearable devices, microsampling, and AI can help minimize patient burden while effectively evaluating the potential for PD.

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INTRODUCTION

Physical dependence (PD) arises from the body adapting to repeated drug exposure and is characterized by withdrawal signs and symptoms (WS) when treatment is abruptly stopped or substantially reduced (FDA, 2017).[1]

- PD and WS occur with both scheduled (eg, opioids, benzodiazepines) and unscheduled drugs (eg, antidepressants, beta-blockers).
- Withdrawal symptoms vary by drug class and include headache, anxiety, nausea, tremors, cognitive impairment, sleep, and mood disturbances.
- WS can range from mild to severe (eg, seizures, suicidality) depending on the drug.[2,3]

The FDA requires PD evaluation as part of abuse potential assessments for new CNS-active drugs to inform labeling for discontinuation risks (and tapering needs) under 21 CFR 201.57, and scheduling recommendations under the Controlled Substances Act (CSA; 21 U.S.C. 811(c)(7).

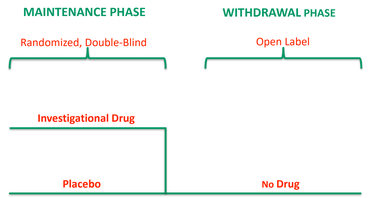
Key regulatory guidance include FDA (2017, 2019)[1,4] and EMA (2006)[5] documents on dependence and labeling.

The FDA's clinical PD evaluation recommendations apply to CNS-active new molecular entities and to drugs containing substances already controlled under the CSA.

In Phase III efficacy trials, PD is typically evaluated via a monitored discontinuation following at least 28 days of chronic dosing (**Figure 1**).

- Observation must last at least five half-lives post-discontinuation.
- Dedicated healthy-volunteer studies or animal models may be used if patient discontinuation is unsafe or WS are expected to be severe.

Figure 1. Withdrawal Phase in a Typical Randomized, Double-Blind Efficacy/Safety Study



Challenges with PD assessments include:

- Patient non-compliance with frequent, clinician-rated withdrawal and disease-specific scales
- Limitations of AE monitoring and physiologic/PK sampling requiring in-clinic visits
- Lack of validated, self-administered scales and tapering guidance

There is a need to adapt study designs – leveraging emerging technologies and novel scales – to capture withdrawal across the full timeframe of interest.

METHODS

In February 2024, ISCTM formed a Physical Dependence Working Group comprised of (n =18) industry and academic experts who meet regularly to:

1. Review current FDA PD evaluation recommendations
2. Identify limitations of existing requirements
3. Propose alternative methods, emerging technologies, and pragmatic study designs

The group evaluated FDA-recommended endpoints to pinpoint those necessitating in-clinic, clinician-administered assessments, then proposed daily, patient-centered alternatives:

- Subject-rated withdrawal scales
- Remote administration of clinician-rated, disease-specific scales via telemedicine
- Physiological and vital-sign monitoring using wearable devices

Additional discussions focused on:

- Early withdrawal-related AE detection and prediction
- Integrating PD assessments earlier in development to inform tapering strategies and regulatory waivers
- The potential role of AI in customizing symptom banks and AE prediction

RESULTS

Approaches Identified

- Sample schedule provided in **Table 1**.

Table 1. Sample Time and Events Schedule for the Assessment of Drug Withdrawal Symptoms in a Phase II/III Clinical Trial

Assessment	Treatment Visit(s)[1]	Drug Discontinuation Phase[2]				
		Drug Discontinuation Day 0	Days 1-6	Follow-Up Day 7	Days 8-20	Final Visit Day 21
Vital Signs (eg, BP, HR, RR, SpO_2)[3]	x	x		x		x
Adverse events	Collected throughout					
C-SSRS[3]	x	x		x		x
Physical examination (symptom directed)	x	x		x		x
ECG[3]	x	x		x		x
Concomitant medications	Collected throughout					
Clinical Laboratory (chemistry, hematology, urinalysis)[3]	x	x		x		x
Drug Withdrawal Scale(s)[3]	x	x	x	x	x	x
Rebound Assessments[3]	x	x		x		x
Visual Analog Scales (Mood/Withdrawal Symptoms)	x	x	x	x	x	x
Pharmacokinetic Blood Sample[3]		x		x		x
Biomarker Sample (if applicable)[3]	x	x		x		X

Abbreviations: BP = blood pressure; C-SSRS = Columbia-Suicide Severity Ratine Scale; ECG = electrocardiogram; RR = respiratory rate; SpO_2 = blood oxygen saturation.

1. Baseline assessments may need to be obtained prior to treatment start and/or prior to study drug discontinuation, as appropriate.
2. Drug discontinuation phase duration and in-clinic visits will need to consider drug pharmacology and clinical trial capacity. The FDA requires an observation duration of at least 5 half-lives of the investigational drug.
3. Assessments require clinician oversight and therefore appear on in-clinic days; alternative modalities of collection eg, wearable devices, subject-rated measures, microsampling, may be considered to enable more frequent collection.

Withdrawal Scales

- Many scales (8/10) are clinician-rated and drug-class specific (**Table 2**).
- A Comprehensive Drug Withdrawal Scale (CDWS) is being developed to:
  - Allow self-administration and frequent use
  - Cover broad symptoms intended to complement AEs, vitals, and PK data (**Table 3**)
  - Include AI-driven customization adapted to drug properties to predict most relevant AEs

Table 2. Clinician- and Subject-Rated Scales Evaluating Signs and Symptoms of Withdrawal Associated with Specific Drug Classes

Scale	Drug Class	Clinician Rated	Subject Rated
Clinical Opiate Withdrawal Scale (COWS)	Opioid	x	
Subjective Opiate Withdrawal Scale (SOWS)	Opioid		x
Physicians Withdrawal Checklist (PWC-20 and PWC-34)	Benzodiazepines / Drugs that affect GABA	x	
Benzodiazepine Withdrawal Symptom Questionnaire	Benzodiazepines	x	
Clinical Institute Assessment of Withdrawal Benzodiazepines (CIAW-B)	Benzodiazepines	x	
Ashton Rating Scale	Benzodiazepines	x	
Amphetamine Withdrawal Scale (AWQ)	Amphetamine	x	
Cocaine Selectivity Severity Assessment (CSSA)	Cocaine	x	
Cannabis Withdrawal Scale	Cannabis		x
Discontinuation Emergent Signs and Symptoms Checklist (DESS)	SSRIs	x	

Abbreviations: GABA = gamma-aminobutyric acid; SSRI = Selective Serotonin Reuptake Inhibitor

Table 3. Drug-Related Effects, Adverse Events and Corresponding Withdrawal Symptoms Presented for Several Drug Classes that Exhibit Physical Dependence

Drug Class	Common Adverse Event/ Drug Effect	Corresponding Withdrawal Symptom
Opioids	Constipation	Diarrhea
	Analgesia	Abdominal Cramping/Pain
	Pupil constriction	Pupil dilation
	Drowsiness	Restlessness/Agitation
Stimulants	Insomnia	Hypersomnia
	Decreased appetite	Increased appetite
Benzodiazepines	Antiepileptic	Seizures/tremors
	Anxiolytic	Anxiety, fear

Disease-Specific Scales

- Often clinician-rated and not optimized for frequent use.
- Telemedicine-based assessments may be employed when rebound symptoms warrant additional monitoring.

Adverse Events (AEs)

- Daily AE collection via ecological momentary assessment (EMA) is feasible but requires context (eg, concomitant medications, health changes) and clinician oversight for coding
- A CDWS-linked predictive AE database is in development.

VAS Scales

- Mood and physical symptoms are EMA-compatible for frequent use.

Physiological Measures

- Non-invasive wearables (eg, ECG, PPG, SCG, bio-impedance) enable remote monitoring of vital signs and other parameters.
- FDA issued staged guidelines for qualification of Medical Device Development Tools[6] and is beginning to accept ambulatory ECG data for NDA support,[7] pending validation (Medical Device Readiness Levels - MDRL 6)[8,9] and device qualification.
- *Limitations*:
  - Most devices remain consumer-grade and require further validation in diverse populations
  - FDA has cleared multiple devices for use (eg, Apple Watch, Masimo W1TM, ANNE One, Bodyguardian MINI, Zio Patch, Dreem 3S).
- AI-driven analytics are critical to interpret large data volumes. Next steps include RCT validation, protocol development, and AI algorithm refinement.

Pharmacokinetic (PK) Sampling

- Microsampling devices (eg, Mitra cartridges) allow remote, low-volume blood collection with validated analytical correlation to venous methods.
- Telehealth support can mitigate compliance issues.
- Samples are mailed for central analysis.

Additional Considerations

- Use multiple-ascending dose studies for early PD data collection.
- Reserve titration/tapering in Phase III for signals detected in Phase II.
- Early PD evaluation may support end-of-phase-II (EOP2) regulatory waivers.

CONCLUSIONS

- Traditional PD data collection methods fall short in capturing withdrawal in patients abruptly discontinued from treatment.
- Early PD data is critical for regulatory decision-making at EOP2.
- Most tools require in-clinic, clinician-administered procedures and are not patient-friendly.
- New technologies and adapted scales facilitate remote, frequent monitoring of withdrawal signs and symptoms.
- The ISCTM group proposes several approaches for efficient, time-sensitive evaluation of drug withdrawal and proactive AE identification.

Disclosures: The viewpoints expressed are those of the authors and not their respective employers. The authors report no conflicts of interest for this work.

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