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Pragmatic Considerations for the Application of Physical Withdrawal Assessments in Patient Studies

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ABSTRACT

AIM: Proposed methodological approach for the appropriate use and interpretation of outcome measures to assess signs and symptoms of physical drug withdrawal in pivotal patient efficacy studies.

METHODS: The evaluation of physical dependence and identification of withdrawal symptoms following abrupt discontinuation of an investigational product are important aspects of its clinical safety profile in addition to its abuse potential assessment under the Controlled Substances Act. Most novel CNS active drugs in development will require an evaluation of physical dependence. While not all drugs that produce physical dependence are abused (e.g., corticosteroids), withdrawal symptoms can manifest with varying severity and can, in some cases, even be life-threatening. Evaluating physical dependence and potential tapering strategies are, therefore, critical to the drug safety information for both providers and patients. Typically, withdrawal symptoms are assessed in phase 2/3 safety and efficacy studies, during the follow-up period once the study drug has been discontinued, or as part of a randomized withdrawal design. As the evaluation of withdrawal depends on frequent assessments of adverse events and withdrawal symptoms, the burden of frequent clinic visits can be an important limiting factor to a comprehensive assessment. Furthermore, some of the measures used to evaluate withdrawal, such as the Clinical Opiate Withdrawal Scale, were originally developed and validated in drug-abusing populations, thus such scales may potentially not be germane to the patient population of interest and may not be appropriate for drugs with novel mechanisms of action. Improving assessment tools, including adaptation of withdrawal scales to ensure comprehension and validity in non-drug abusing patients and identification of the relevant AEs of interest, is important for the accurate collection of data that will inform on the physical dependence potential of an investigational product.

CONCLUSION: A comprehensive approach to the assessment of physical dependence will be presented.

INTRODUCTION

Physical dependence is a state of physiological adaptation following repeated drug use that manifests withdrawal signs and symptoms after abrupt discontinuation or significant drug dose reduction[1]. Withdrawal from some medications, including antidepressants, benzodiazepines, opioids, and stimulants, can trigger severe outcomes[2] including suicidality. Therefore, assessing physical dependence can be an important CNS-active drug development component for understanding the potential benefit-risk to patients.

The assessment of physical dependence can serve 2 distinct yet often conflated purposes:

1. Adds to the establishment of the drug's general safety profile and the potential need for tapering at discontinuation, providing important information for providers and patients, and
2. Factors into the assessment of the abuse potential (AP) of the drug and the need for scheduling.

Physical dependence and addiction are often used interchangeably; however, these are distinct phenomena.

- While addiction involves compulsive drug use despite adverse consequences, dependence signifies the body's adaptation to a substance, leading to withdrawal symptoms upon cessation.
- Drugs that cause physical dependence[3] may or may not have AP (e.g., antidepressants, beta-blockers).
- Currently, physical dependence is addressed only in the FDA guidance on the assessment of the AP of CNS-active drugs[4].

The evaluation of physical dependency is generally evaluated in a clinical trial in one of two ways:

1. During a phase 2/3 patient study following abrupt discontinuation of the study drug or
2. In a dedicated phase 1 study in normal healthy volunteers, an approach best suited for drugs targeted for patient populations that cannot be studied in a drug-absent state (e.g., seizure disorders).

Adding onto phase 2/3 studies enables the evaluation of rebound effects (worsening of underlying pathology) related to drug withdrawal since it involves the target patient population and offers efficiencies for sponsors. Yet the assessment of physical dependence in such studies using current methodologies presents both scientific and pragmatic challenges. These challenges will be discussed next.

OBJECTIVE

To present a methodological framework for using and interpreting outcome measures to evaluate signs and symptoms of physical drug withdrawal in key patient efficacy studies.

DISCUSSION

In phase 2/3 clinical settings, a comprehensive approach to evaluate physical dependence and withdrawal symptoms should address:

- Operational considerations such as correct identification of withdrawal types (new symptoms, persistent, rebound[5]) and ability to differentiate withdrawal from relapse or recurrence of the original illness.
- Sufficient treatment duration for the pharmacologic effect of the drug to be well-established for the development of dependence and for the full range of withdrawal types to manifest.
- Sufficient duration of the withdrawal period to capture signs and symptoms of physical dependence.
- Determination of the timing of baseline assessments.
- Frequency of each assessment.
- Potential complications of concomitant/rescue medications.
- Compliance with self-reported assessments.
- Appropriate Pharmacodynamic (PD) and pharmacokinetic (PK) evaluations.
- Statistical analysis considerations.

Current methodologies for the assessment of physical dependence, as noted in the FDA guidance, include the following components:

- Drug class-specific withdrawal scales (e.g., VAS assessing withdrawal symptoms and mood states)
- Disease-specific scales for evaluation of potential symptom rebound
- Assessment of AEs before and after drug discontinuation
- Daily diaries maintained by study participants
- Physiological measures and vital signs
- Assessment of the association of PK and withdrawal signs/symptoms

Implementation of many of these components into phase 2/3 studies can present pragmatic challenges.

General Considerations

- A major challenge of phase 2/3 studies is their outpatient nature, which poses limitations on the feasibility of frequent in-clinic visits and implementation of procedures that require clinician oversight (e.g., blood sampling, clinician-administered scales/questionnaires).
- The evaluation of physical dependence prolongs the study, which poses an additional burden on participants and is further exacerbated by numerous assessments.
- Insufficient sampling of symptoms based on the drug's half-life and active metabolite formation limits the fulsome characterization of the chronology of various withdrawal syndromes (acute, protracted, and rebound). Insufficient data points can also limit statistical analysis conclusions and underestimate the effect sizes needed to determine whether statistically significant findings are also clinically important.
- Depending on the disease under study, Principal Investigators and trial staff may be unfamiliar with many of the assessments performed.

Withdrawal Scales

- If the drug under study falls into a known drug class, a validated withdrawal scale[4] could be used (**Table 1**), but if the drug is a novel compound, some or none of the scales may be optimal.
- Many withdrawal and disease-specific scales are clinician-administered, requiring in-person or remote interaction with a clinician, which is impractical when daily assessments are required for an extended period.
- Most current validated scales were originally developed and validated in drug-abusing populations, which can complicate the evaluation of dependence and withdrawal syndromes for molecular entities with multiple or novel mechanisms of action and relevant patient populations. Moreover, the terminology/concepts may not be understood or relevant for non-drug users (e.g., intense cravings, needing to take the drug more frequently, increased irritability, anxiety, feeling like "coasting" or "pleasantly sick")[6].

Diaries/Telephone Screening

- Can be utilized in higher frequencies than assessments requiring clinician administration and/or requiring clinic visits, and can also be used to supplement scheduled clinic visits.
- Quality depends on patient compliance and reliability for self-reporting.
- Other limitations include potential challenges in interpreting and quantifying events that are not evaluated in the clinic.

Table 1. Illustration of pharmacodynamic measures evaluating withdrawal symptoms classified by drug class, psychiatric conditions, and physiological status

Drug Withdrawal	Scale	Self-Rated Y/N
Drug Class		
Opiates	Clinical opiate withdrawal scale	N
	Subjective opiate withdrawal scale	Y
Benzodiazepines	Physician withdrawal checklist (PWC-20; PWC-34)	N
	Tyrer's benzodiazepine withdrawal symptom questionnaire	Y
	Benzodiazepine dependence questionnaire	Y
	Clinical institute assessment of withdrawal-benzodiazepines	Y
Stimulants	Amphetamine withdrawal questionnaire	N
	Cocaine selective severity assessment	Y
Cannabinoids	Cannabis withdrawal scale	Y
	Marijuana withdrawal checklist	Y
SSRIs	Discontinuation emergent signs and symptoms checklist	Y
Psychiatric Conditions		
Depression and Suicidality	Columbia-suicide severity rating scale	N
	Profile of mood state - bipolar	Y
	Hamilton depression rating scale	Y
	Montgomery-åsberg depression rating scale	Y
	Beck depression inventory	Y
	Hospital anxiety and depression scale	Y
Anxiety	Hamilton anxiety rating scale	Y
	Spielberger state anxiety inventory, short form	Y
Sleep	Pittsburgh sleep quality index	Y
	Epworth sleepiness scale	Y
Cognition	Hopkins verbal learning test-revised	N
	Divided attention test	Y
	Digit-symbol substitution task	Y
	Subject-rated visual analogue scales (VAS)	Y
	Anxiety VAS	Y
	Sick VAS	Y
	Pain VAS	Y
	Nausea VAS	Y
Psychosis	Positive and negative syndrome scale for schizophrenia	Y
	Brief psychiatric rating scale	Y/N
Physiological Status		
	Vital Signs	N
	Pupil diameter	N
	Respiratory rate	N
	Arterial oxygen saturation	N
	Skin temperature	N
	Systolic and diastolic blood pressure	N
	Heart rate	N

Table 2. Sample time and events schedule for a 3-week drug discontinuation phase conducted following abrupt drug discontinuation in a phase 2/3 trial.

Assessment	Treatment Visit(s)[1]	Drug Discontinuation Phase				
		Drug Discontinuation Day 0	Days 1-6[2]	Follow-Up Day 7	Days 8-20[2]	Final Visit Day 21
Vital Signs (e.g., BP, HR, RR, SpO_2)	x	x		x		x
Adverse events[3]	←	Collected throughout				→
C-SSRS	x	x		x		x
Physical examination (symptom directed)	x	x		x		x
ECG	x	x		x		x
Concomitant medications[3]	←	Collected throughout				→
Clinical Laboratory (chemistry, hematology, urinalysis)	x	x		x		x
Drug Withdrawal Scale(s)[4]	x	x	x	x	x	x
Rebound Assessments[5]	x	x		x		x
Pharmacokinetic Blood Sample		x		x		x
Biomarker Sample (if applicable)	x	x		x		x

Abbreviations: BP = blood pressure, HR = heart rate, RR = respiratory rate, SpO_2 = oxygen saturation
[1] Treatment visit assessments serve as baseline for the evaluation of withdrawal symptoms.
[2] Data collection on non-visit days conducted remotely via completion of patient e-diary or telephone screening.
[3] Collected throughout using e-diary or telephone screening.
[4] Drug withdrawal scales amenable to self-reporting may be administered throughout. Scales requiring clinician assessment may be limited to administration on Visit days. Scales to be administered once daily.
[5] Rebound assessments include scales, questionnaires, or clinical assessments to evaluate population pathology, typically primary and key secondary study endpoints.

Physiological Measures and Vital Signs

- These measures require frequent assessments.
- If relevant, physical withdrawal metrics include specialized physiological measures like pupil diameter or skin temperature (**Table 1**), which may be unfamiliar to investigators and require specific training and/or purchase of specialized equipment.

Collection of Adverse Events

- Adverse events associated with the signs and symptoms of physical dependence will be dependent on the pharmacology of the drug under study and may be influenced by the patient population.
- There is an absence of a drug withdrawal AE term within the Common Terminology Criteria for Adverse Events (CTCAE v5.0). Clinical trials require investigators to document an overall clinical diagnosis of drug withdrawal and maintain a separate record of AE-related symptoms with graded severity.
- Provisions need to be made to analyze AEs during drug treatment separately from those during the follow-up/discontinuation period.
- The discrepancies between spontaneously reported AEs and symptom endorsement on PD questionnaires can pose challenges for safety data analysis.

Despite these challenges, with early planning and potential modifications to these standard assessments, high-quality data can be collected with minimized inconvenience to investigators and participants.

- An example of a pragmatic approach that could be considered for a phase 2/3 clinical trial is illustrated in a time and events schedule (**Table 2**).
- Recognition of potential withdrawal effects early in drug development can enhance the evaluation of dependence and withdrawal during phase 2/3 clinical trials. Nonclinical data can be leveraged, particularly for novel compounds.
- To alleviate the inconvenience of in-clinic visits, incorporating self-administered scales and questionnaires via apps on electronic devices provided to subjects or their own cellular phones might be considered. Exploration of blood sampling kits that may be performed at home for drug concentration analysis may be considered if such analytical methods can be performed for a given drug.
- The specificity of PD scales originally developed and validated in drug-abusing populations can complicate the evaluation of dependence and withdrawal syndromes for molecular entities with multiple or novel mechanisms of action and relevant patient populations. The development of validated, novel, self-administered withdrawal scales may help to address these limitations[6]. Inclusion of measures validated for different drug classes[7] and psychiatric conditions should be adopted to capture the full constellation of potential withdrawal symptoms. Additionally, PD questions specifically linked to drug abuse instead of disease state may need to be adapted to use more understandable and non-stigmatizing terminology and promote accurate reporting of symptoms.
- Teasing out the potentially serious AEs associated with different types of withdrawal syndromes will require astute observations of behavioral changes to be coupled with appropriately sampled PK data, physiological parameters, easy-to-understand PD measures, and improved AE data collection.
- Presentation of effect size should accompany statistically significant correlations of PK-PD-Safety endpoints to help inform clinically meaningful decisions.

CONCLUSIONS

In conclusion, Physical dependence remains an underrecognized medical problem that can lead to concerning, even dangerous, drug discontinuation effects. Therefore, the evaluation of physical dependence in clinical trials is important for improving drug safety and understanding the potential benefit-risk to patients.

Pragmatic approaches to include frequent assessments of drug withdrawal symptoms are needed for large patient studies.
Incorporating insights from non-clinical studies, clinical considerations, and regulatory guidance is necessary to develop robust methodologies and comprehensive assessments to identify dependence signals.

Modifications to current methodologies and the use of technological advances could make it easier to implement physical dependence assessments within clinical trials and improve the quality and interpretability of the data obtained.

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

References

[1] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry - assessment of abuse potential of drugs. Silver Spring, MD 20993-0002; 2017.
[2] Chouinard G, Samaha AN, Chouinard VA, Peretti CS, Kanahara N, Takase M, et al. Antipsychotic-induced dopamine supersensitivity psychosis: pharmacology, criteria, and therapy. Psychother Psychosom 2017; 86: 189–219.
[3] APA. Diagnostic and statistical manual of mental disorders, 5th Edition: DSM-5. 5th edn. Arlington, VA: American Psychiatric Publishing; 2013.
[4] 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.
[5] Chouinard G, Chouinard VA. New classification of selective serotonin reuptake inhibitor withdrawal. Psychother Psychosom 2015; 84:63–71.
[6] Setnik, B, Milovan D. Development of the Subject-Rated Comprehensive Drug Withdrawal Scale (CDWS) to Evaluate the Physical Dependence Potential of Investigational Drugs. The College on Problems of Drug Dependence (CPDD) 86th Annual Scientific Meeting. 2024, Jun 15-19; Montreal QC: M123 https://cpdd.societyconference.com/cont#sessions/conf10005
[7] Reidenberg MM. Drug discontinuation effects are part of the pharmacology of a drug. J Pharmacol Exp Ther 2011; 339: 324–8.