Review of measures to evaluate drug withdrawal for CNS-active drugs

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- *All content in this talk regarding views/opinions/observations/ comments expressed by us is entirely that of our own and does not necessarily reflect the views/opinions of our employers.*

Overview

- Review of withdraw assessments
  - MedDRA SMQ for withdrawal
  - Spontaneous discontinuation adverse events
  - Structured discontinuation scales or checklists
  - Other measures of withdraw

- Considerations for New Molecular Entity Development

Drug classes with identified withdrawal symptoms

- Opiates
- Stimulants
- Benzodiazepines
- Antidepressants
- Anti-psychotics
- Ketamine
- Testosterone and androgenic anabolic steroids
- Beta-blockers
- Corticosteroids

Lyrica

9.3 Dependence

In clinical studies, following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including **insomnia, nausea, headache or diarrhea** *[see Warnings and Precautions (5.8)]*, consistent with physical dependence. In the postmarketing experience, in addition to these reported symptoms there have also been reported cases of **anxiety and hyperhidrosis**

Prozac

Dependence

PROZAC has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the premarketing clinical experience with PROZAC did not reveal any tendency for a withdrawal syndrome or any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of PROZAC (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Vyvanse

Dependence

Physical dependence (a state of adaptation manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) may occur in patients treated with CNS stimulants including **Vyvanse**. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include extreme **fatigue and depression.**

MedDRA SMQ for Withdrawal

- Standardized *MedDRA Query diagnostic criteria
  - "Drug withdrawal" SMQ (broad and narrow) captures only overt or diagnosed withdrawal syndrome
  - Too blunt for clinical trials

Drug withdrawal convulsions	Drug rehabilitation
Drug withdrawal headache	Rebound effect
Drug withdrawal maintenance therapy	Steroid withdrawal syndrome
Drug withdrawal syndrome	Withdrawal arrhythmia
Drug withdrawal syndrome neonatal	Withdrawal syndrome

*Medical Dictionary for Regulatory Activities

Assessment of Discontinuation AEs

- A broad of list of predefined terms can be used as part of routine AE review
  - Most frequently reported discontinuation symptoms will likely be related to pharmacological class/activity and disorder under study
- List of AE terms assessing withdrawal following abrupt drug discontinuation (N=25 terms)

Agitation	Depression	Early morning awakening	Morose	Pain
Anhedonia	Diarrhoea	Feeling of despair	Nausea	Poor quality sleep
Anxiety	Dysphoria	Headache	Negative thoughts	Syncope
Chills	Dyssomnia	Hyperhidrosis	Nervousness	Tremor
Depressed Mood	Dysthymic disorder	Insomnia	Obsessive thoughts	Vomiting

Approaches to Capture Spontaneous AE

- Defining and summarizing emergence of AEs after cessation of treatment
  - All AEs emerging after cessation of treatment
  - To minimize "noise" can be defined as AEs that are not present during 7 days before cessation/tapering of treatment
- Importance of parsing out AEs and re-emergence of symptoms of primary disorder
  - Use of efficacy scale (eg MADRS, HAM-A) may be useful here
  - Relapse designs

Approaches to Capture Spontaneous AE

- Follow-up period determined by pharmacokinetic properties of treatment (ie half-life)

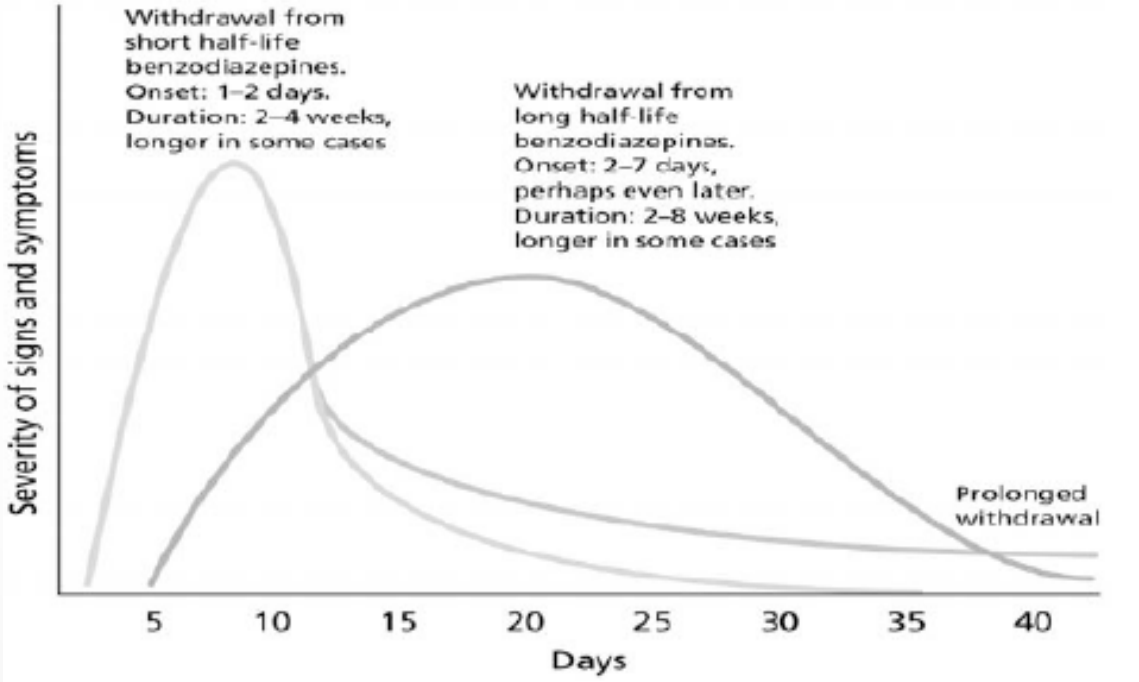

Figure 1: Symptoms and duration of benzodiazepine withdrawal

Source: NSW Health (2008, p.30)

Select Withdrawal Scales

- Most checklists or structured scales are devised from retrospective review of AEs reported on discontinuation
  - **Opiates withdrawal scales**
    - Clinical Opiate Withdrawal Scale (COWS)
    - Subjective Opiate Withdrawal Scale (SOWS)
    - Objective Opiate Withdrawal Scale (OOWS)
  - **Benzodiazepines withdrawal scales:**
    - Physicians Withdrawal Checklist PWC-20 and PWC-34
    - Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ)
    - Clinical Institute Assessment of Withdrawal Benzodiazepines (CIAW-B)
    - Ashton Rating Scale
  - **Stimulants withdrawal scales:**
    - Amphetamine Withdrawal Questionnaire (AWQ)
    - Cocaine Selective Severity Assessment (CSSA)
  - **Cannabinoids withdrawal scale:**
    - Cannabis Withdrawal Scale
  - **SSRI withdrawal scale**
    - Discontinuation Emergent Signs and Symptoms Checklist (DESS)

PWC-20

General similarities across withdrawal scales

- Physical symptoms
  - GI effects
  - Autonomic symptoms
  - Weakness, motor symptoms
  - Headaches
- Mood symptoms
  - Anxiety
  - Sleep disturbances
  - Psychiatric disturbances, including perceptual distortion and cognitive symptoms
  - Sensory and visual disturbances

Similarities across withdrawal scales within a class

- Comparison of benzodiazepine scales

	Ashton rating scale (1991)	CIWA-B (Busto et al 1989)	PWC (Rickels et al 1990)	BWSQ (Tyrer et al 1990)
GI Symptoms	√		√	√
Autonomic symptoms	√	√	√	
Anxiety symptoms	√	√	√	√
Psychiatric disturbances	Unreality, obsessions, depression, paranoia, hallucinations	Obsessions	Depersonalisation, depression, paranoia, hallucinations	Feeling unreal, depression, hallucinations
Sleep disturbance	√	√	√	
Motor Symptoms	√ stiffness	√ Muscle aches or stiffness	√	√

Similarities across withdrawal scales within a class

	Ashton rating scale (1991)	CIWA-B (Busto et al 1989)	PWC (Rickels et al 1990)	BWSQ (Tyrer et al 1990)
Headache	√	√	√	
Fits	√		√	
Paresthesias	√	√	* In PWC-20	√
Weakness Drowsiness / Fatigue	√	√	√	
Perceptual distortion	√		√	√
Cognitive symptoms	√ + ataxia	√	√	√
Sensory disturbances	√ (light, taste, smell)	√	√	√ + peculiar taste
Visual disturbances	√	√		

Similarities across withdrawal scales between drug classes

- 18 of 20 Physician Withdrawal Checklist (PWC-20) items overlap with Discontinuation Emergent Signs and Symptoms Checklist (DESS)

Subjective vs. objective measures of withdrawal

- Subjective scales: subject experience (symptoms: feel hot, feel cold)
  - May be preferable because severe subjective symptoms may occur when objective symptoms are mild or absent
  - Example: Subjective Opiate Withdrawal Scale (SOWS)
- Objective scales: observer reported (signs: vomiting, tremors)
  - Objective scales with observable "signs" are sometimes considered more reliable than patient reported symptoms
  - Most objective scales do not capture variables that change over time or that require some baseline assessment, such as changes in weight, heart rate, blood pressure, respiratory rate or pupillary diameter
- Some scales include evaluation of both a patient's signs or symptom.
  - Example: Clinical Opiate Withdrawal Scale (COWS)

Patient vs. clinician rated scales

- Many symptoms of withdrawal are not readily observable or occur at intervals and may be missed by the observer

Interpretation of scores

- Need to understand scoring system and clinical interpretation

  - **Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ):** Change score of 3 or greater from baseline indicates withdrawal.
  - **Clinical Institute Assessment of Withdrawal Benzodiazepines CIWA-B (0-80)**
    - 1–20 = mild withdrawal
    - 21–40 =moderate withdrawal
    - 41–60 = severe withdrawal
    - 61–80 = very severe withdrawal

Validation of measures

- High test-retest reliabilities
- High internal consistencies
- Concurrent validity
- Convergent validity with other validated measures

Other measures useful in evaluation of withdrawal

- Subject-rated Visual Analogue Scales (VAS):
  - Anxiety VAS
  - Sick VAS
  - Nausea VAS

- Physiological Measures:
  - Pupil diameter
  - Respiratory rate (RR)
  - Arterial oxygen saturation
  - Skin temperature
  - Systolic and diastolic blood pressure (SBP and DBP)
  - Heart rate (HR)

Other measures useful in evaluation of withdrawal

- Depression Scales
  - Hamilton Depression Rating Scale (HDRS)
  - Montgomery-Asberg Depression Rating Scale (MADRS)
  - Beck Depression Inventory
- Anxiety Scales
  - Hamilton Anxiety Rating Scale (HAM-A)
  - Spielberger State Anxiety Inventory (SSAI) Short-form
- Sleep scales
  - Pittsburgh Sleep Quality Index (PSQI)
  - Leeds Sleep Evaluation Questionnaire (LSEQ)
- Profile of Mood State - Bipolar (POMS-Bi)
- Hopkins Verbal Learning Test – Revised (HVLT-R)
- Divided Attention Test (DAT)
- Digit-Symbol Substitution Task (DSST)

Considerations for New Molecular Entity Development

- Importance of understanding drug-specific withdrawal symptom propensity
  - Preclinical Physical Dependence and Withdrawal study
  - Pharmacokinetic properties important to consider
- Understanding of AE profile upon cessation of treatment can help to guide scale choice or prospective review of AEs of interest

Conclusions

- With no “gold standard” discontinuation scale, reviewing discontinuation adverse events remains an appropriate method to assess for withdrawal symptoms
- Structured Scales or Checklists have utility for quantifying symptoms or comparing between treatments
- Pharmacological class of compound is important in determining appropriate scale or prospective definitions of discontinuation symptoms

Thank you