Evaluation of Dependence and Withdrawal in Clinical Trials and Human Dependence Study - Design and Considerations

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Disclosure

The opinions and information in this presentation are those of the author and do not necessarily reflect the views and policies of the FDA.
The proposed definition of Addiction:

A biological state that may develop after repeated abuse of a substance, which increases the desire of using the drug over time despite of harmful consequences, as well as the possibility of the development of tolerance or development of physical dependence (as manifested by a withdrawal syndrome).
The proposed Definition of Physical Dependence:

- A state in which the body adapts to the drug, requiring a higher amount of it to achieve a certain effect (tolerance) and eliciting drug-specific physical or mental symptoms if drug use is abruptly ceased (withdrawal).

- It is associated with the repeated use of both known drugs of abuse and drugs with no abuse potential.

  (For example, the “propranolol withdrawal syndrome” may cause the increased blood pressure temporarily higher than that prior to beginning the medication, headache, chest pain, and palpitations and sweating.)
DSM-V Diagnostic Criteria
Substance-Induced Disorders
Substance Intoxication and Withdrawal
Example: Sedative, Hypnotic Withdrawal

Sedative, Hypnotic, or Anxiolytic Withdrawal

Diagnostic Criteria

A. Cessation of (or reduction in) sedative, hypnotic, or anxiolytic use that has been prolonged.

B. Two (or more) of the following, developing within several hours to a few days after the cessation of (or reduction in) sedative, hypnotic, or anxiolytic use described in Criterion A:
   1. Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 bpm).
   2. Hand tremor.
   3. Insomnia.
   4. Nausea or vomiting.
   5. Transient visual, tactile, or auditory hallucinations or illusions.
   6. Psychomotor agitation.
   7. Anxiety.

C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Specify if:
The discontinuation/withdrawal syndrome consists of 2 clinical aspects:

1) recurrence of symptoms of the treated disorder in patients, sometimes more severe
   (This would be one important reason to evaluate dependence in healthy subjects)

2) discontinuation/withdrawal effect: which can include other signs and symptoms, which typically do not represent a relapse of the underlying condition, but are related to the disruption of neuro-regulatory changes established during drug administration.

The specific symptom profile of discontinuation syndromes depends on the pharmacology and pharmacokinetics of the drug being administered and neurotransmitter system affected.
Why is human dependence study needed?

1. **CSS concern relates to 21 USC 812 (b):**

   If the drug is a controlled substance or will be scheduled, we monitor abuse of the controlled substances and assess new data that relates to abuse and dependence liability resulting from abuse.
Why is the human dependence study needed?

2. **Dependence/withdrawal data is also needed:**

- To inform physicians and patients whether or not the DRUG can be abruptly withdrawn at the end of treatment.

- To inform subjects abusing the DRUG about health consequences of the development of dependence and consequences of DRUG withdrawal.

- And, to inform physicians and institutions providing treatment to subjects abusing the DRUG about specific adverse events which can occur as consequences of abrupt DRUG withdrawal.
Known withdrawal syndromes in different drug classes

- Opiates
- Benzodiazepines
- Stimulants (amphetamine, cocaine, methamphetamine)
- Ketamine
- Club drugs (MDMA, heroine)
- Testosterone and androgenic anabolic steroids (AAS)
- Antidepressants (“Prozac withdrawal syndrome”)
- Anti-psychotics (Quetiapine, Clozapine)
- Beta-blockers and clonidine
- Corticosteroids
Withdrawal syndromes – examples
(in red are serious adverse events)

• **Opiate withdrawal syndrome**
  - Yawning, rhinorrhea, lacrimation, mydriasis, piloerection, vomiting, tremors, weight loss
  - Increases in pulse, blood pressure, temperature, and respiratory rate, drug craving, anxiety, irritability, muscle and bone aches, hot and cold flashes, nausea, and abdominal cramps

• However, serious but rare symptoms may occur such as: cardiac arrhythmias, dehydration, seizures, stroke, suicide attempt, violent behavior
Withdrawal syndromes – Scheduled drugs-examples

(in red are serious adverse events)

• **Benzodiazepine C-IV withdrawal syndrome**

  o Seizures, psychosis, suicide, homicidal ideation

  o Irritability, increased tension and anxiety and tremor, sweating, dry retching and nausea, difficult concentration, palpitations, severe sleep disturbance, hallucinations

  o Panic attacks, confusion and cognitive difficulty, memory problems, weight loss, headache, muscular pain and stiffness, and perceptual changes.
Withdrawal syndromes – Scheduled drugs – examples
(in red are serious adverse events)

• **Stimulants withdrawal syndrome**
  
  o Dysphoric mood, depression, paranoia, violence, aggression, irritability, suicidality
  
  o Shivering or chills, anxiety, marked reduction in energy, psychomotor retardation or agitation, insomnia or hypersomnia, increased appetite, aches and pains, impaired social functioning
  
  o Fatigue, vivid, unpleasant dreams, compulsive craving.
Withdrawal syndromes – Scheduled drugs-
examples
(in red are serious adverse events)

- **Testosterone C-III withdrawal syndrome**
  - Depressed mood, major depressions, suicidal ideation and suicides
  - Fatigue, craving, restlessness, anorexia, insomnia
  - Decreased libido and suppression of the hypothalamic-pituitary-testicular (HPT) axis with hypogonadotrophic hypogonadism.
Withdrawal syndromes – NOT scheduled drugs-examples
(in red are serious adverse events)

• Beta-blockers withdrawal syndrome- BB rebound phenomenon
  
  o Heart palpitations, accompanied by shortness of breath
  
  o Profuse sweating, wheezing, severe headache, body pain, nausea, vomiting, worsening angina (chest pain), and intense abdominal cramping
  
  o Sharp rise in blood pressure, heart attack or sudden death.
Withdrawal syndromes –NOT Scheduled Drugs
(in red are serious adverse events)

• **Antidepressant withdrawal syndrome**
  
  o Agitation, anxiety, aggression, insomnia
  
  o Electric shock-like sensations (“brain zaps”), akathisia, panic attacks, irritability, dysphoria
  
  o Hyperactivity, dizziness, nausea, vomiting, headache, chills, body aches, paresthesias, depersonalization
  
  o Delirium, delusions, suicidality, homicidality
Withdrawal syndromes - NOT Scheduled Drugs-
examples
(in red are serious adverse events)

• **Corticosteroids withdrawal syndrome**
  - Acute adrenal insufficiency, hypotension, circulatory collapse
  - Fatigue, anorexia, nausea, vomiting, diarrhea, abdominal pain, weakness, fever

• **Clonidine withdrawal syndrome**
  - Acute hypertensive crisis, myocardial infarction
  - Tachycardia, tremor, headache, anxiety, agitation, vomiting
Relatively new arrival on withdrawal syndrome list

- **Dopamine agonist withdrawal syndrome (DAWS)**
  - Syndrome described in patients who are withdrawn from long-term treatment with dopamine agonists (DA).
  - Described by Rabinak and Niremberg 2010 in patients with Parkinson's disease (PD), where most were withdrawing DA because of the development of impulse control disorders (ICD).
  - It presents as a constellation of neuropsychiatric and autonomic symptoms: depression, anxiety, agoraphobia, fatigued, dysphoria, irritability, agitation, pain, sleep disturbances, diaphoresis and orthostatic hypotension and drug cravings.
Factors possibly influencing formation of drug dependence

- Time of exposure
- Dose
- Drug potency
- Neurotransmitter system affected (ex: opiate vs serotonin)
- Gender
- Age
- Individual neuro-physiological make-up
- Other factors
The length of exposure necessary for development of dependence

Example: Benzodiazepines- formation of dependence


Dependence forms in:

• 4-8 weeks – chlorodiazepoxide (*100-600 mg qd)
• 4-6 weeks – lorazepam (*2 mg q 2hr)
• 6-12 weeks – diazepam (*40-80 mg qd)
• 6 weeks – oxazepam (*400-600 mg qd)

*However excessively high doses often were used in these cases of “short-term withdrawal”
Dependence Studies in Healthy Volunteers


Dependence Studies in Patients


Dependence Studies in Children


Opioid (buprenorphine, morphine) dependence study


Design:

• The study is within-subject, in not-treatment seeking opioid-dependent healthy volunteers (N=7) who were stabilized on either buprenorphine (32 mg/day i.m.) or morphine (120 mg/day i.m.) given in four divided doses for 9 days.

• Duration: 59 days, in research unit.

• The subjects underwent an 18-day period of spontaneous withdrawal, during which four double-blind i.m. placebo injections were administered daily.

• Opioid withdrawal measures were collected 8 times daily (30 min before and after im dose) and a once daily participants also completed a set of cognitive tasks.
Opioid (buprenorphine, morphine) dependence study

**Assessments:**

- Clinical Opiate Withdrawal Scale (COWS)
- Subjective Opioid Withdrawal Scale (SOWS)
- Visual Analog Scale (VAS) for good, bad effects, sick and pain (0–100)
- Profile of Mood States (POMS)
- Digit Symbol Substitution Task (DSST)
Opioid dependence study

Assessments (cont):

- **Assessments of sleep included:**
  - Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)
  - Insomnia Severity Index (ISI; Bastien et al., 2001).
  - The PSQI and ISI were modified to be collected once a week

- **Physiologic measures:**
  - respiratory rate (RR)
  - arterial oxygen saturation
  - skin temperature
  - systolic and diastolic blood pressure (SBP and DBP)
  - heart rate (HR)
  - pupil diameter
Opioid dependence study

COWS and SOWS

POMS: mood/pain

Fig. 2. Mean Peak Daily Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS) ratings (+ S.E.M.) during and after active drug cessation.
Opioid dependence study

Results:

- **Morphine withdrawal** symptoms were significantly greater than those of **buprenorphine withdrawal** as measured by mean peak ratings of:
  1) Clinical Opiate Withdrawal Scale (COWS): max day 2
  2) Subjective OpiateWithdrawal Scale (SOWS): max day 2
  3) All subscales of the Profile of Mood States (POMS) max: total mood disturbance on day 2-3
  4) Visual Analog Scales, mean peak: sick rating - day 1; pain rating - day 2
  5) VS: systolic and diastolic blood pressure:
    - mean peak SBP and DBP occurred on day 2
    - mean peak HR occurred on day 5
  6) Pupil dilation: occurred rapidly during morphine withdrawal, and stabilized by day 2

- **Buprenorphine withdrawal**:
  - Little evidence of withdrawal was seen during the 18 days after cessation of buprenorphine.

Conclusions:

- Morphine withdrawal peak ratings on COWS and SOWS occurred on day 2 of and were significantly greater than on day 2 of buprenorphine withdrawal.
- Subjective reports of morphine withdrawal resolved on average by day 7.
- Spontaneous withdrawal from high-dose buprenorphine appears subjectively and objectively milder compared with that of morphine for at least 18 days after drug cessation.
Population:

- Healthy volunteers, age 18-55 y.o.
- or relevant to the indication age group, such as elderly > 55 y.o. if drug is developed for Alzheimer or Parkinson disease
- or patient population if the disorder targeted by the drug does not include neuro-psychiatric symptomatology (ex: peripheral neuropathy)
- Number of subjects who completed the study should be adequate to show statistical significance...

Gender:

- 50% females and 50% males, especially important when there are gender differences in PK or adverse events profile
Evaluation of dependence in pediatric population – current Agency view

Statement of Pediatric and Maternal Health Staff and PREA regulations

• Dependence study **should not** be performed in pediatric population.

• The study should be performed in adult population, only.

• The results of the study in adults should be extrapolated using data from dependence study in animals (2 arms design with juvenile and adult groups to compare potential differences due to age, and including placebo).
Human Dependence Study - Design

**Dose:**

- Highest tolerated therapeutic dose
- The dose should not be changed during the maintenance period (drug administration period) unless some subjects do not tolerate the highest dose but tolerate lower dose
- Placebo arm should be included
- During the withdrawal period placebo should be used for both arms drug and placebo to blind for potential effect of withdrawal
Human Dependence Study - Design

- **Treatment time:** ~ 4 weeks, depends on T1/2 and time to steady state, the time on steady state should be at least 3 weeks

- **Time of withdrawal:** At least 5 times half-life plus 1-2 weeks
  - (to ~0 drug plasma levels), total ~14-30 days (as inpatient)

- **PD Scales-administration time points**
  - Baseline
  - Last day on drug
  - First day of discontinuation
  - Then depends on T1/2 but generally first 2-3-5 day, then every 3 days, but maybe daily, too, depends on drug
Human Dependence Study- Design

- **AEs collection:**
  - During the treatment phase and the withdrawal phase, reported separately

- **Blood sampling: for PD-PK correlation:**
  - **Time points:** to follow the PD time-points
  - **Rationale for PK evaluation:**
    - to distinguish between AEs due to drug toxicity or underlying disorder vs withdrawal
    - the symptoms are sometimes identical, so, PK is critical to provide clarification

**Example 1:** nausea/vomiting - one of the most common AE due to drug toxicity, but also very common withdrawal symptom

**Example 2:** in epilepsy population seizure after drug withdrawal could be a part of the disorder or could be withdrawal seizures
Available Withdrawal Scales

• **Opiates withdrawal scales**
  – Clinical Opiate Withdrawal Scale (COWS)
  – Subjective Opiate Withdrawal Scale (SOWS)

• **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)
Helpful scales used in dependence evaluation

**It is recommended that already validated scales are used**

- **Columbia-Suicide Severity Rating Scale (C-SSRS)**
- **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)**
Other helpful measures used in dependence evaluation

Subject-rated Visual Analogue Scales (VAS):

- Anxiety VAS
- Sick VAS
- Pain 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)
Ethical Issues related to Human Dependence Studies

Our viewpoints:

• This is a part of the evaluation of drug safety, which in some cases is critically important, especially, if the drug has to be abruptly withdrawn due to serious, life-threatening adverse events.

• Human dependence study should be considered another Phase 1 or 2 study.

• A large number of dependence studies (as noted previously), has been performed, in healthy subjects and in patients.
Conclusions

1. It is still preferable that dependence and withdrawal are evaluated after chronic drug use in Phase 1 and 2 and human dependence studies are to be used only in absence of such data.

2. The sponsor should plan such studies in advance, even in pre-IND stage and contact the Agency on how to implement evaluation of dependence and withdrawal during Phase 1 and Phase 2 clinical studies.

3. The collection of withdrawal AEs from all clinical studies is still required, and it is easy to obtain, because after every clinical study there is a follow-up visit.
Concluding Sentence

From:

“Given the experience with the benzodiazepines, we believe the regulatory bodies should have required studies from the manufacturers that could have elucidated the dependence potential of the SSRIs before marketing authorization was granted”.

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Questions for discussion

1. What should be the study population, patients or healthy volunteers?

2. Should the study attempt to produce dependence and measure the withdrawal or rather mimic the clinical scenario (time factor?)

3. What length of time is the most appropriate for the study and how to find out how quickly the dependence would develop:
   • Is 4 week period enough to form dependence in healthy volunteers/patients?
   • Should this time period be longer?
   • Should depend on drug characteristic?

4. Should the dose be the highest therapeutic or supra-therapeutic to compensate for relative short time of exposure?
Thank you
Back-up Slides
DSM-V
Substance-Induced Disorders
Substance Intoxication and Withdrawal

- Criteria for **substance withdrawal** are included within the substance-specific sections of this chapter.

- **Criterion A.** The essential feature is the development of a substance-specific problematic behavioral change, with physiological and cognitive concomitants, that is due to the cessation of, or reduction in, heavy and prolonged substance use.

- **Criterion C.** The substance-specific syndrome causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

- **Criterion D.** The symptoms are not due to another medical condition and are not better explained by another mental disorder.

- Withdrawal is usually, but not always, associated with a substance use disorder. Most individuals with withdrawal have an urge to re-administer the substance to reduce the symptoms.
WHO Definition of dependence

- In 1964, the WHO Expert Committee on Drug Dependence introduced "dependence" as "A cluster of physiological, behavioral and cognitive phenomena of variable intensity, in which the use of a psychoactive drug (or drugs) takes on a high priority".

- The necessary descriptive characteristics are preoccupation with a desire to drug-seeking behavior and some other problematic consequences in biological, psychological or social activities.
Six characteristic features of drug dependence

1. A strong desire or sense of compulsion to take the drug

2. Difficulties in controlling drug-taking behavior in terms of its onset, termination, or levels of use

3. A physiological withdrawal state when drug use is stopped or reduced: Evidence: A characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance relieves or prevents further withdrawal symptoms
Six characteristic features of drug dependence (cont)

4. **Evidence of tolerance**: increased doses of the drug are required in order to achieve effects originally produced by lower doses.

5. **Progressive neglect of alternative pleasures or interests because of drug use**: increased the amount of time necessary to obtain or take the drug or to recover from its effects.

6. **Persisting with drug use despite clear evidence of overtly harmful consequences**: such as harm to the liver, depressive mood states or impairment of cognitive functioning.
Withdrawal syndromes – Scheduled drugs- examples
(in red are serious adverse events)

• **Ketamine C-III withdrawal symptoms**
  
  o Paranoia, Suicidal or violent tendencies, Psychosis
  
  o Depression, chills, intense cravings, restlessness, nightmares, anxiety, tremors, sweating, irregular and rapid beating of the heart, tiredness, decreased appetite. aggression and hostility
Withdrawal syndromes - Not Scheduled Drugs-examples

• **Anti-psychotic withdrawal syndrome (Quetiapine)**

- Nausea, emesis, lightheadedness, diaphoresis, dyskinesia, orthostatic hypotension
- Tachycardia, insomnia, nervousness, dizziness, headache, excessive non-stop crying, and anxiety.

In **Seroquel XR study AEs of insomnia**, nausea, headache, diarrhea, vomiting, dizziness and irritability did not exceed *5.3%* in any treatment group and usually resolved after 1 week post-discontinuation. However, gradual withdrawal was advised.

*In spite of relatively low number of patients with symptoms of withdrawal, this information is included in the label.*
 Withdrawal syndromes – NOT scheduled drugs-examples
(in red are serious adverse events)

• **Anti-psychotic withdrawal syndrome (Clozapine)**
  
  o Severe, rapid-onset of psychotic symptoms including delirium

  o Cholinergic rebound effects such as nausea, vomiting, diarrhea, headache, restlessness, agitation, and sweating

  o Severe movement disorders, dystonia, dyskinesia
Benzodiazepines dependence study


**Design:**

- The effect of abrupt discontinuation of therapeutic doses of short half-life and long half-life benzodiazepines was examined in 57 benzodiazepine-dependent patients (daily use, >1 year) over a three-week stabilization period.

- All patients were being treated with either the long half-life (LHL) benzodiazepines diazepam or clorazepate dipotassium, or with the short half-life (SHL) to intermediate half-life derivatives lorazepam or alprazolam.

- There were 3 arms: placebo for LHL-BZ group, placebo for SHL-BZ group, and continuation of BZ treatment.

- Clinical assessments were performed daily for 8 days, including benzodiazepine plasma levels at baseline, and daily during the experimental week. All patients on placebo continued to receive double-blind placebo medication for 4 subsequent weeks. Final assessments were performed at 5 week.
Benzodiazepines dependence study

Assessments

- For anxiety: the Hamilton Rating Scale for Anxiety (HAM-A)\(^1\)9 and the anxiety factor of the 80-item Hopkins Symptom Checklist (HSCL)\(^2\)0
- For depression: the Hamilton Rating Scale for Depression 21 and the depression factor of the HSCL
- For benzodiazepine withdrawal: 34-item Physician Withdrawal Checklist

Results

- Approximately 58% to 100% of patients experienced a withdrawal reaction, with a peak severity at 2 days for short half-life and 4 to 7 days for long half-life BZ.
- The severity of withdrawal was related to:
  - Shorter half-life
  - Higher dosage
  - Faster falling BZ plasma levels
Benzodiazepines dependence study

**Physician Withdrawal Checklist - total score**
- solid line with triangles indicates long half-life
- solid line with circles, short half-life
- solid line with squares, controls

**Days to peak severity of withdrawal-PWC**
- hatched bars indicate short half-life benzodiazepine treated group
- closed bars, long half-life benzodiazepine-treated group
Example of dependence study in healthy non-dependent subjects


Study Design:

Population: 9 male subjects (age range 21-39 years)

Treatments-Duration: 56-day double-blind study with random assignment to initial treatment A or B
  • A - zopiclone 7.5 mg p.o. nightly for 21 days followed by placebo for 7 days
  • B - placebo nightly for 21 days followed by placebo for 7 days

Assessments of withdrawal-results:
  • Heart rate, blood pressure, hand tremor and auditory-evoked EEG were repeatedly measured during the withdrawal periods.
  • No differences in any of these variables between phases were found
  • Subjects slept longer (mean 28 min, p less than 0.013) on zopiclone than on placebo
  • Unfortunately, no BZ withdrawal scales were administered…but it’s only 1983!
Zopiclone dependence study, cont.

Assessments (cont.):

- Subjects slept longer (mean 28 min, p less than 0.013) on zopiclone than on placebo.

- Symptoms of state anxiety were greater on days 2 and 4 after discontinuing zopiclone compared to all other withdrawal days. The mean relative increase on days 2 and 4 was 30%.

- Sleep depth (self-rating scale) was no deeper on drug than on placebo, but during the withdrawal phases, sleep was less deep on days 2 and 4 of withdrawal from zopiclone compared to all other withdrawal days.

- Subjects were unable to identify the pattern of drug administration on withdrawal, and none reported important symptoms.

- Discontinuation of zopiclone (7.5 mg for 21 days) is associated with detectable increase in state anxiety and lighter sleep on days 2 and 4 of withdrawal.
Dependence Study in Schizophrenia Patients


**Design:**

- **Subjects:** 30 patients who met DSM-III-R criteria for schizophrenia, residual type, or schizophrenia in remission were enrolled in the study

- **Duration:** 28-day inpatient stay

- **Treatment:** clozapine 200 mg/day

- Withdrawal effects after abrupt discontinuation from clozapine were evaluated for 7 days
Dependence Study in Schizophrenia Patients

**Results:**

- 11/28 subjects had no withdrawal symptoms.
- 12 had mild withdrawal adverse events of agitation, headache, or nausea.
- 4 experienced moderate withdrawal adverse events of nausea, vomiting, or diarrhea.
- 1 patient experienced a rapid-onset psychotic episode requiring hospitalization.
- Cholinergic rebound is a likely explanation for the mild to moderate withdrawal symptoms and is easily treated with an anticholinergic agent.
References


References cont.


