Regulatory perspective in evaluating drug withdrawal symptoms in clinical trials

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Session:

Assessments Physical Dependence in Clinical Setting

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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

Definition of Physical Dependence

by CDER Working Group, Aug 2012

The proposed Definition of Physical Dependence (not referring to Addiction)*:*

- *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

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.**

DSM-V Diagnostic Criteria

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.
8. Grand mal seizures.

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:

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: include new signs and symptoms, which typically do not represent a relapse of the underlying condition, but are related to the disruption of neuro-regulatory changes (neuroadaptation) 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.

Definitions

- **Neuroadaptation** refers to the process whereby the body compensates for the presence of a chemical in the body so that it can continue to function normally.

- **Withdrawal is a reversal of neuroadaptation**

  Withdrawal symptoms tend to be the opposite of the effects produced by the presence of the drug in the body.

Why is information on human dependence needed?

1. Concern relates to 21 USC 812 (b):

For scheduling, the CSA requires a finding on relative abuse potential and relative dependence liability.

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 from abuse.

Why is the information on human dependence needed?

2. Dependence data is addressed in Section 9.3 of label:

- To inform physicians about consequences of abrupt withdrawal at the end of treatment or about tapering to avoid potentially dangerous symptoms after abrupt withdrawal of the DRUG
- To inform physicians of dangers and consequences of abrupt withdrawal which might be necessary due to occurrences of serious adverse events caused by the DRUG, unexpected drug-drug interactions or due to lack of efficacy
- 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
- Drug abusers are also informed about health consequences of dependence development and consequences of DRUG withdrawal

Known withdrawal syndromes in different drug classes

- Opiates
- Benzodiazepines
- Stimulants (amphetamine, cocaine, methamphetamine)
- Antidepressants (“Prozac withdrawal syndrome”)
- Anti-psychotics (Quetiapine, Clozapine)
- Beta-blockers
- Corticosteroids
- Testosterone and androgenic anabolic steroids (AAS)
- Ketamine
- Club drugs (MDMA, heroine)

Withdrawal syndromes – examples

(in red are serious adverse events)

- **<u>Opiate C-II withdrawal syndrome</u>**
  - 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)

- **<u>Benzodiazepine C-IV withdrawal syndrome</u>**

  - Seizures, psychosis with hallucinations and delusions, suicide, homicidal ideation, coma

  - insomnia, hyperosmia, dizziness, headache, anorexia, muscular pain and stiffness, tremor, sweating, nausea and vomiting, tachycardia and palpitations, postural hypotension

  - Panic attacks, irritability, anxiety, confusion and cognitive difficulty, memory problems, hallucinations

Withdrawal syndromes –Scheduled drugs- examples

(in red are serious adverse events)

- **Stimulants withdrawal syndrome**

  - Dysphoric mood, depression, paranoia, violence, aggression, irritability, suicidality
  - Shivering or chills, anxiety, marked reduction in energy, psychomotor retardation or agitation, insomnia or hypersomnia, increased appetite, aches and pains, impaired social functioning
  - Fatigue, vivid, unpleasant dreams, compulsive craving.

Withdrawal syndromes –Scheduled drugs- examples

(in red are serious adverse events)

- **<u>Testosterone C-III withdrawal syndrome</u>**

  - 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 hypogonadotropic hypogonadism.

Withdrawal syndromes –NOT scheduled drugs- examples

(in red are serious adverse events)

- **<u>Beta-blockers withdrawal syndrome- BB rebound phenomenon</u>**

  - Heart palpitations, accompanied by shortness of breath
  - Profuse sweating, wheezing, severe headache, body pain, nausea, vomiting, worsening angina (chest pain), and intense abdominal cramping
  - Sharp rise in blood pressure, heart attack or sudden death.

Withdrawal syndromes –NOT Scheduled Drugs

(in red are serious adverse events)

- **<u>Antidepressant withdrawal syndrome</u>**

  - Agitation, anxiety, aggression, insomnia
  - Electric shock-like sensations (“brain zaps”), akathisia, panic attacks, irritability, dysphoria
  - Hyperactivity, dizziness, nausea, vomiting, headache, chills, body aches, paresthesias, depersonalization
  - Delirium, delusions, suicidality, homicidality

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

MacKinnon GL, Parker WA. Benzodiazepine **withdrawal** syndrome: a literature review and evaluation. *Am J Drug Alcohol Abuse*. 1982;9(1):19-33. Review.

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"**

Generally, the higher the dose and the longer the benzodiazepine is taken, the greater the risk of developing withdrawal symptoms.

However, withdrawal symptoms may occur in patients receiving recommended doses and/or short-term therapy.

Clinical Assessment of Dependence

Population:

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

Dose:

1. Highest tolerated therapeutic dose
2. Placebo arm should be included
3. During the withdrawal period placebo should be used for both arms drug and placebo to blind for potential effect of withdrawal

Clinical Assessment of Dependence/ Human Dependence Study

- **Treatment time**: ~ 4 weeks, depends on T1/2 and time to steady state (~3weeks)
- **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, 1st day of discontinuation, Then varies with T1/2
- **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**:
    - Distinguish between AEs due to drug toxicity or underlying disorder vs withdrawal
    - Symptoms are sometimes identical, so PK is critical to provide clarification
  - **Example 1**: nausea/vomiting - common AE in drug toxicity, and but in W/D
  - **Example 2**: in epilepsy population seizure after drug withdrawal could be due to the disorder or a withdrawal symptom

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

- 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 (ex. agranulocytosis, seizures, myocarditis caused by Clozapine)

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

- A large number of dependence studies, has been performed, in healthy subjects and in patients, adult and children, as well

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 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:

Nielsen M1, Hansen EH, Gøtzsche PC**. Dependence and withdrawal reactions to benzodiazepines and selective serotonin reuptake inhibitors. How did the health authorities react?** Int J Risk Saf Med. 2013;25(3):155-68.

"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".

Thank you

Back-up Slides

Questions regarding clinical evaluation of dependence

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

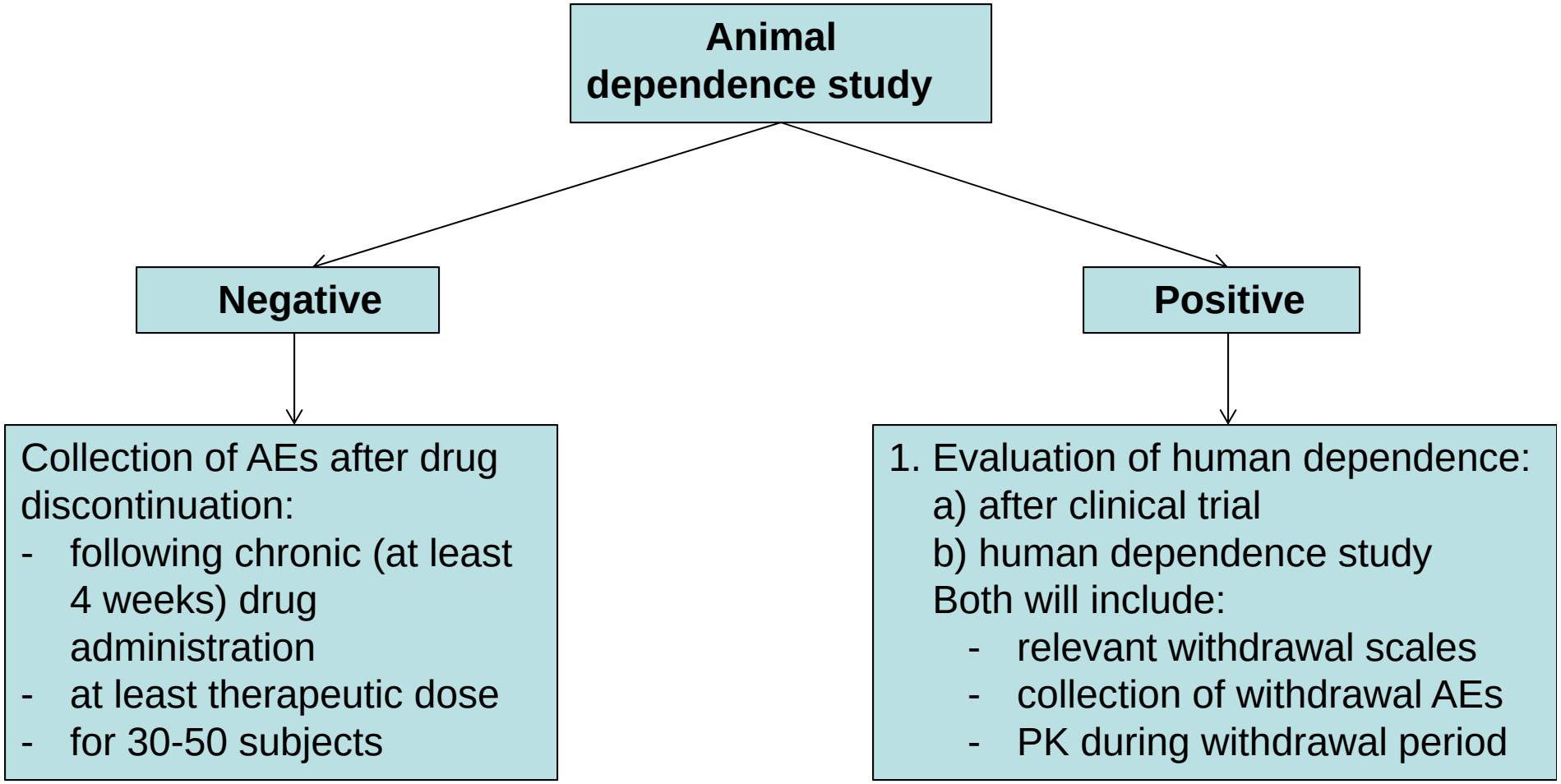
2. Should the study attempt to produce dependence and measure the withdrawal or rather mimic the clinical scenario (time factor?)

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?

4. Is MedDRA search for dependence related adverse events helpful or all adverse events during the withdrawal period should be evaluated especially for NMEs?

Proposed decision tree for evaluation of dependence



Evaluation of dependence in pediatric population – <u>current</u> 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.
- If the human dependence study is positive in adults the results of the study should be extrapolated using data from dependence study in juvenile animals (arm with juvenile and adult groups to compare potential differences due to age, and include placebo arms).

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

- **Anti-psychotic withdrawal syndrome (Clozapine)**
  - severe, rapid-onset of psychotic symptoms including delirium
  - cholinergic rebound effects such as nausea, vomiting, diarrhea, headache, restlessness, agitation, and sweating
  - severe movement disorders, dystonia, dyskinesia

Dependence Studies in Healthy Volunteers

- **1980- Loperamide, nufenoxole:** Dependence liability of two antidiarrheals, nufenoxole and loperamide. Korey A, Zilm DH, Sellers EM. Clin Pharmacol Ther. 1980 May;27(5):659-64.
- **1993-Zopiclone:** Evaluation of zopiclone physical dependence liability in normal volunteers**.** Dorian P, Sellers EM, Kaplan H, Hamilton CPharmacology. 1983;27 Suppl 2:228-34
- **2010-Tramado**l; Psychopharmacology (Berl). 2010 Sep;211(4):457-66. doi: 10.1007/s00213-010-1919-3.Physical dependence potential of daily tramadol dosing in humans. Lanier RK1, Lofwall MR, Mintzer MZ, Bigelow GE, Strain EC. (*healthy-opioid dependent*)
- **2013- Morphine-buprenorphine**: A double blind, within subject comparison of spontaneous opioid withdrawal from buprenorphine versus morphine.. JTompkins DA, Smith MT, Mintzer MZ, Campbell CM, Strain EC Pharmacol Exp Ther. 2014 Feb;348(2):217-26. doi: 10.1124/jpet.113.209478. (*healthy-opioid dependent*)

Dependence Studies in Patients

- **1961-Librium:** Hollister LE, Motzenbecker FP, Degan RO. Withdrawal reactions from chlordiazepoxide ("Librium"). Psychopharmacologia. 1961 Feb 20;2:63-8. (***patients; anxiety, schizophrenia***)
- **1991- Benzodiazepines**: Long-term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation. Rickels K, Schweizer E, Case WG, Greenblatt D. JArch Gen Psychiatry. 1990 Oct;47(10):899-907. ***(pts on chronic BZ)***
- **1996-Clozapine**: Shiovitz TM1, Welke TL, Tigel PD, Anand R, Hartman RD, Sramek JJ, Kurtz NM, Cutler NR. Cholinergic rebound and rapid onset psychosis following abrupt clozapine withdrawal. Schizophr Bull. 1996;22(4):591-5. (***schizophrenia patients)***
- **2008-SSRI-Venlafaxin**e: Tint A1, Haddad PM, Anderson IM. The effect of rate of antidepressant tapering on the incidence of discontinuation symptoms: a randomised study. J Psychopharmacol. 2008 May;22(3):330-2. doi: 10.1177/0269881107087488. (***major depressive disorder***)
- **2008-BZ**; Rickels K, Garcia-Espana F, Mandos LA, Case GW (2008) Physician Withdrawal Checklist (PWC-20). J Clin Psychopharmacol 28:447-451 (***anxiety disorders)***

Dependence Studies in Children

- **Fentanyl-1994:** Katz, R., H. W. Kelly, et al. "Prospective study on the occurrence of withdrawal in ***critically ill*** children who receive fentanyl by continuous infusion." Critical Care Medicine 22(5): 763-767..
- **Atomoxetine-2004**: Wernicke, J. F., L. Adler, et al. (2004). "Changes in Symptoms and Adverse Events after Discontinuation of Atomoxetine in Children and Adults with ***Attention Deficit/Hyperactivity Disorder***: A Prospective, Placebo-Controlled Assessment." Journal of Clinical Psychopharmacology 24(1): 30-35.
- **Steroids-2005**: Saracco, P., N. Bertorello, et al. (2005). "Steroid withdrawal syndrome during steroid tapering in childhood ***acute lymphoblastic leukemia***: A controlled study comparing prednisone versus dexamethasone in induction phase." Journal of Pediatric Hematology/Oncology 27(3): 141-144.
- **Modafinil-2006**: Swanson, J. M., L. L. Greenhill, et al. (2006). "Modafinil film-coated tablets in children and adolescents with ***attention-deficit/hyperactivity disorder***: Results of a randomized, double-blind, placebo-controlled, fixed-dose study followed by abrupt discontinuation." Journal of Clinical Psychiatry 67(1): 137-147.
- **Cannabis-2008**: Milin, R., I. Manion, et al. "Prospective assessment of cannabis withdrawal in adolescents with ***cannabis dependence***: A pilot study." Journal of the American Academy of Child and Adolescent Psychiatry 47(2): 174-179.