Strategies for Discontinuing Hypnotic Use

OHSU Psychiatry Grand Rounds
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Learning Objectives: The successful participant in this training will be able to:

1. Describe three strategies for discontinuing hypnotic use
2. Compare outcome results of the three strategies to routine care
3. Identify four factors which affect withdrawal planning

I. FDA Drug Safety Communication (1.10.13)

[http://www.fda.gov/Drugs/DrugSafety/ucm334033.htm#tabs-3]

A. FDA urges health care professionals to caution all patients (men and women) who use these zolpidem products about the risks of next-morning impairment for activities that require complete mental alertness, including driving. For zolpidem products, data show the risk for next-morning impairment is highest for patients taking the extended-release forms of these drugs (Ambien CR and generics). Women appear to be more susceptible to this risk because they eliminate zolpidem from their bodies more slowly than men

B. Driving simulation and laboratory studies recently submitted to FDA indicate that zolpidem blood levels above approximately 50 ng/mL appear capable of impairing driving to a degree that increases the risk of a motor vehicle accident. In pharmacokinetic trials of 10 mg Ambien (or bioequivalent zolpidem products) that included approximately 250 men and 250 women, about 15% of women and 3% of men had zolpidem concentrations that exceeded 50 ng/mL approximately 8 hours post-dosing. Three measurements in women and one in men were ≥90 ng/mL at about 8 hours after use.

C. A higher percentage of both men and women experience potentially impairing morning zolpidem levels after use of extended-release zolpidem products (Ambien CR or generic equivalents). In pharmacokinetic trials of zolpidem extended-release 12.5 mg, approximately 33% of women and 25% of men had zolpidem blood concentrations exceeding 50 ng/mL approximately 8 hours post-dosing. About 5% of patients had blood levels ≥100 ng/mL.

D. In studies of zolpidem extended-release 6.25 mg, at 8 hours after dosing, about 15% of adult women and 5% of adult men had a zolpidem level of ≥50 ng/mL, whereas for both elderly men and women, about 10% had such a zolpidem level.

II. AASM Clinical Guidelines (Schutte-Rodin, et al., 2008)

A. "Short term hypnotic treatment should be supplemented with behavioral and cognitive therapies when possible.

B. When pharmacotherapy is utilized, the choice of a specific pharmacological agent within a class should be directed by:

1. Symptom pattern
2. Treatment goals
3. Past treatment responses
4. Patient preferences
5. Cost
6. Availability of other treatments
7. Comorbid conditions
8. Contraindications
9. Concurrent medication interactions
10. Side effects

C. For patients with primary insomnia (psychophysiologic, idiopathic or paradoxical ICSD-II subtypes) when pharmacologic treatment is utilized alone or in combination therapy, the recommended general sequence of medication trials is

1. Short-intermediate acting BZD receptor agonists (BZD or newer BzRAs) or ramelteon: examples of these medications include zolpidem, ezopiclone, zaleplon, and temazepam

2. Alternate short-intermediate acting BzRAs or ramelteon if the initial agent has been unsuccessful
3. Sedating antidepressants, especially when used in conjunction with treating comorbid depression/anxiety: examples of these medications include Trazodone, amitriptylene, doxepin, and mirtazapine
4. Combined BzRA or ramelteon and sedating antidepressant
5. Other sedating agents: examples include anti-epilepsy medications (gabapentin, tiagabine) and atypical antipsychotics (quetiapine and olanzapine)

    a) These medications may only be suitable for patients with comorbid insomnia who may benefit from the primary action of these drugs as well as from the sedating effect

D. Over-the-counter antihistamine or antihistamine/analgesic type drugs (OTC 'sleep aids') as well as herbal and nutritional substances (e.g., valerian and melatonin) are not recommended in the treatment of chronic insomnia due to the relative lack of efficacy and safety data (p. 488)"

III. Definitions

A. Abuse (DSM-IVTR)

1. Failure to fulfill major role obligations
2. Use in situations that are physically hazardous
3. Legal problems
4. Social or interpersonal problems

B. Dependence (DSM-IVTR)

1. Tolerance
2. Withdrawal
3. Larger amounts/longer periods than intended
4. Persistent desire/unsuccessful cut down
5. Time investment
6. Social, occupational, recreational activities curtailed
7. Continued use despite negative effects

C. Discontinuation

1. Drug specific
2. Disorder specific

IV. Insomnia vs. Panic Conceptualization

A. Shared

1. Safety Behaviors (Salkovskis, 1991)
2. Anxiety Sensitivity (Reiss, 1991)

B. Insomnia

1. Biology

    a) Circadian rhythms
    b) Sleep homeostat

2. PPP Model

    a) Predisposing factors
    b) Precipitating factors
    c) Perpetuating factors

3. Treatment goal: improved sleep efficiency

C. Panic

1. Fear of fear cycle
2. Treatment goal: wolves

v. Treating Anxiety vs. Treating Panic

A. Otto & Pollack (2009)

1. Cognitive Restructuring
2. Interoceptive Exposure
3. Relaxation Training

B. Perlis, et al., (2008)

1. Sleep Hygiene
2. Perpetuating Factors
3. Sleep Restriction
4. Sleep Compression
5. Stimulus Control
6. Cognitive Restructuring

v. Insomnia Relevant Research

A. BZD discontinuation in older adults with chronic insomnia (**Morin, et al., 2004**)

1. 76 older adults with prolonged use of BZD for insomnia, randomly assigned to 10 week taper, CBT-I, or combined
2. 63% were drug free at end of treatment; proportion of drug free patients significantly higher in combined group
3. average dose of BZD decreased and frequency of use decreased
4. absence of significant rebound insomnia during withdrawal period
5. sleep improvements were modest initially and became more noticeable at follow-ups

FIGURE 1. Weekly Quantity of Benzodiazepine Medication Used by Older Adults With Insomnia in a Randomized Clinical Trial of Three Interventions to Facilitate Benzodiazepine Discontinuation

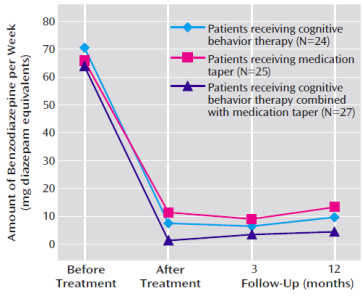
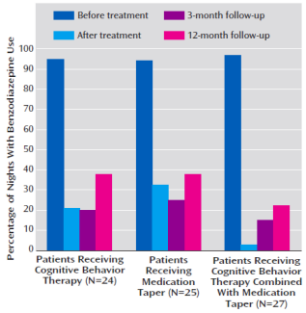


FIGURE 2. Percentage of Nights With Benzodiazepine Use Among Older Adults With Insomnia in a Randomized Clinical Trial of Three Interventions to Facilitate Benzodiazepine Discontinuation



B. Ambien users vs. non-users with CBT-I (**Zavesicka, et al., 2008**)

1. 15 patients who had received Ambien for at least 1 year prior to the study and were successively withdrawn during weeks 2 – 6 of an 8 week of group CBT-I compared to 13 patients who had not used hypnotics
2. Both groups demonstrated improved sleep
   a) TST
   b) REM sleep time
   c) Sleep efficiency
3. Medication group had significantly more improvement in SE and WASO

C. Taper alone vs. taper with self help CBT-I (**Belleville, et al., 2007; Belleville & Morin, 2008**)

1. 53 chronic insomniac hypnotic users (34 females) (BZD, zopiclone or zaleplon 3 nights / week for at least 3 months) undergoing hypnotic withdrawal
2. CBT-I = 5 booklets about 15 pages each
3. No group differences 6 months after intervention conclusion
4. Less than 1/3 maintained drug free status at 6 months
5. Another 1/3 discontinued but resumed medication use during the 6 months
6. 1/3 did not reach drug-free status at any time
7. Participants who remained medication free for 6 months
   a) Less severe insomnia
   b) Less severe anxiety
   c) Positive perception of health
   d) Higher self-efficacy

8. No influence on outcome

    a) Dosage
    b) Duration of use
    c) Half-life of pharmacological agent used

9. None of the poly-medicated chronic hypnotic users reached and maintained drug free status

D. CBT-I vs. sham biofeedback in hypnotic-dependent older adults (**Soeffing, et al., 2008**)

7. Treatment group n = 20; control group n = 27; Age over 50; Sustained 6 month use of any prescription medication used specifically to improve sleep

8. 8 sessions individual CBT-I compared to a sham biofeedback treatment

    a) Relaxation b) Stimulus control c) Sleep hygiene

9. CBT-I led to significant improvements in subjective

    a) SOL b) WASO c) SE

10. Not accompanied by comparable gains in daytime functioning

VI. Strategies for BZD Discontinuation

A. Brief interventions – Simple Advice

1. Letter
2. Large group meeting

B. Gradual Dose Reduction

1. 25% dose reduction / week until lowest dose is reached
2. Increasing number of drug free nights

C. Psychological Interventions

1. relaxation training
2. psycho-education for BZD withdrawal
3. teaching strategies to address insomnia

D. Substitutive pharmacotherapy with Gradual Dose Reduction

VII. 2 Meta-analyses: Benzodiazepine Discontinuation

A. Voshaar, et al., 2006

1. 29 studies (22 of which are included in Parr, et al., 2008)
2. RCT, BZD use for 3 months
3. Routine Care vs. Minimal Intervention
4. Routine Care vs. Systematic Discontinuation
5. Routine Care vs. Systematic Discontinuation + CBT
6. Routine Care vs. Systematic Discontinuation + Pharmacotherapy

B. Parr, et al., 2008

1. 32 studies (22 Of which are also included in Voshaar, et al., 2006)
2. Routine Care vs. Brief Intervention
3. Routine Care vs. Gradual Dose Reduction (GDR)
4. Routine care vs. GDR + Psychological Interventions
5. GDR vs. GDR + Psychological Interventions
6. GDR vs. GDR + Pharmacotherapy

VIII. Brief/Minimal Intervention

	OR	95% CI
A. Voshaar (3 studies, 601 subjects):	2.8	1.60 – 5.10
B. Parr (3 studies w/ individuals randomized, 532 subjects):	4.37	2.28 – 8.40
C. Parr (2 studies w/ practices randomized):	2.21	1.92 – 2.55

D. Long term outcome of letter intervention (de Gier, et al., 2011)

1. 163 participants who had discontinued BZD use 3 months after receiving a letter from their physician regarding discontinuation
2. 73% were abstinent or showed minimal use 10 years later
3. 59% appeared to be completely BZD free

IX. Gradual Dose Reduction

A. Voshaar (1 study, 107 subjects)	6.1	2.00 – 18.60
B. Parr (1 study, 107 subjects)	5.96	2.08 – 17.11

X. GDR + Psychological Interventions (relaxation training, psycho-education for BZD withdrawal, teaching strategies to address anxiety and insomnia)

A. Voshaar (2 studies)	5.5	2.3 – 14.2
B. Parr (3 studies, 354 subjects)	3.38	1.86 – 6.12

XI. GDR vs. GDR + Psychological Interventions

A. Parr (7 studies, 454 subjects) at post-cessation	1.82	1.25 – 2.67
B. Parr (6 studies, 308 subjects) at follow-up	1.88	1.19 – 2.97

XII. Withdrawal Assessment

A. Poly-hypnotic use
B. Insomnia severity
C. Anxiety level
D. Self-efficacy

XIII. Treatment Planning

A. Motivation
B. Psychopharmacology
C. What is Sleep?
D. Insomnia Interventions

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