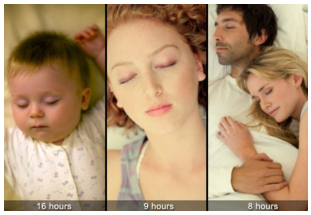

Sleep pills: What and How should we use ?

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Introduction

- Most sleeping pills are classified as "sedative hypnotics."
- That's a specific class of drugs used to induce and/or maintain sleep.
- Sedative hypnotics include benzodiazepines, barbiturates, and various hypnotics

Introduction

key questions before choosing your sleep medicine

- How long does it take for the sleeping pill to take effect?
- How long do the effects last?
- What's the risk of becoming dependent on the sleeping pill, physically or psychologically?

Guidelines for the Use of Sleeping pills

- Define a clear indication and treatment goal
- Prescribe the lowest effective dose
- Limit duration of use to a few weeks
- Individualize the dose for each patient
- Use lower doses in patients also taking a CNS depressant, in the elderly, and in patients with hepatic or renal disorders.

Guidelines for the Use of Sleeping pills

- Avoid if patients have sleep apnea or respiratory disorders or a history of sedative abuse, if they are drinking alcohol, or if they are pregnant
- For patients who need longer-term treatment, consider intermittent therapy
- Avoid abruptly stopping the drug if possible (i.e, taper it)
- Re-evaluate drug treatment regularly; assess efficacy and adverse events

Ramelteon is an exception; it can be given to patients with mild to moderate OSA or COPD or a history of sedative abuse. Low-dose doxepin also has no abuse liability.

Sleeping pills

Scope

- Barbiturates
- Benzodiazepine
- Non-benzodiazepines
- Others
  - Melatonin
  - Antihistamines
  - Antidepressants
  - Antipsychotics
  - Orexin Receptor Antagonists

Barbiturate

- Barbiturates act as CNS depressants, produce a wide spectrum of effects, from mild sedation to total anesthesia
- Effective as anxiolytics, hypnotics, and anticonvulsants. Barbiturates also have analgesic effects;
- Have dependence liability, both physical and psychological
- Barbiturates now largely been replaced by benzodiazepines in routine medical practice, in treatment of anxiety and insomnia
  - because benzodiazepines significantly less dangerous in overdose

Benzodiazepines

- **How It Works**
  - Binds to general GABA receptors in the brain, inhibit NREM stage 1 and 2 sleep), while asleep, drugs disrupt sleep architecture: decreasing sleep time, delaying time to REM sleep, and decreasing deep slow-wave sleep
- **Duration of Effects**
  - Varies (from 4 hours to more than 12)
- **Side Effects**
  - Sedation, loss of muscle coordination, dizziness, habit-forming.
- **Dependence Risk**
  - Higher

Benzodiazepines

- Ativan(lorazepam)
- Halcion(triazolam)
- Restoril(temazepam)
- Valium(diazepam)
- Xanax(alprazolam)

Benzodiazepines

- Benzodiazepines can be useful for short-term treatment of insomnia
- Use beyond 2 to 4 weeks not recommended due to risk of dependence
- It is preferred benzodiazepines be taken intermittently and at the lowest effective dose
- Improve sleep-related problems by shortening time spent in bed before falling asleep, prolonging sleep time, and, reducing wakefulness

Benzodiazepines

- Like alcohol, benzodiazepines are commonly used to treat insomnia in the short-term, but worsen sleep in the long-term
- While benzodiazepines can put people to sleep (i.e., inhibit NREM stage 1 and 2 sleep),
  - while asleep, BZPs disrupt sleep architecture: decreasing sleep time, delaying time to REM sleep, and decreasing deep slow-wave sleep

Benzodiazepines

- Other drawbacks of hypnotics, including benzodiazepines, are
  - Possible tolerance to their effects
  - Rebound insomnia
  - Reduced slow-wave sleep
  - Withdrawal period typified by rebound insomnia and a prolonged period of anxiety and agitation
- Older adults should not use benzodiazepines to treat insomnia unless other treatments failed to be effective

Ativan: LORAZEPAM

- This medication is used to treat anxiety
- Lorazepam belongs to a class of drugs known as benzodiazepines which act on the brain and nerves (central nervous system) to produce calming effect
- This drug works by enhancing effects of a certain natural chemical in the body (GABA)

Valium: DIAZEPAM

- Diazepam is used to treat anxiety, alcohol withdrawal, and seizures
- It is also used to relieve muscle spasms and to provide sedation before medical procedures
- This medication works by calming the brain and nerves
- Diazepam belongs to a class of drugs known as benzodiazepines.

Xanax: ALPRAZOLAM

- Alprazolam used to treat anxiety and panic disorders. It belongs to a class benzodiazepines which act on the brain and nerves (central nervous system) to produce a calming effect by enhancing effects of GABA
- Dosage is based on your medical condition, age, and response to treatment, dose may be gradually increased until the drug starts working well
- This medication may cause withdrawal reactions, especially if used regularly for a long time or in high doses
  - withdrawal symptoms (such as seizures) may occur if you suddenly stop using this medication.
- May rarely cause abnormal drug-seeking behavior (addiction), increased if having abused alcohol or drugs in the past

Drug	Half Life* (h)	Dose†	Comments
Benzodiazepine receptor agonists: Benzodiazepines			
Triazolam	1.5–5.5	0.25–0.5 mg	May cause anterograde amnesia; high likelihood of tolerance and rebound after repeated use
Temazepam	9.5–12.4	7.5–15 mg	Longest latency for sleep induction
Estazolam	10–24	0.5–2 mg	Effective for sleep induction and maintenance
Quazepam	39–100	7.5–15 mg	High lipophilicity, which may mitigate residual sedation in first 7–10 days of continuous use
Flurazepam	47–100	15–30 mg	High risk of next-day residual sedation; not recommended for the elderly

Non-benzodiazepines

- Non-benzodiazepines are a class of psychoactive drugs that are very "benzodiazepine-like" in nature.
- Nonbenzodiazepines pharmacodynamics almost entirely same as benzodiazepine drugs
  - Therefore employ similar benefits, side-effects, and risks
  - Nonbenzodiazepines, however, have dissimilar or entirely different chemical structures, and therefore are unrelated to benzodiazepines on a molecular level
- Examples include
  - zopiclone (Imovane, Zimovane)
  - Eszopiclone (Lunesta)
  - Zaleplon (Sonata)
  - Zolpidem (Ambien, Stilnox, Stilnoct)

Selective GABA Medicines

- **How It Works**
  - Binds to a specific type of GABA receptor in the brain
- **Duration of Effects**
  - 6-8 hours
- **Side Effects**
  - Usually few. Memory disturbances, hallucinations, behavior changes possible.
- **Dependence Risk**
  - Medium (usually low)

Selective GABA Medicines

- **Selective GABA Medicines**
  - Ambien(zolpidem tartrate)
  - Ambien CR (zolpidem tartrate extended release)
  - Lunesta(eszopiclone)
  - Sonata(zaleplon)

Selective GABA Medicines: ZOLPIDEM TARTRATE

- Zolpidem is used to treat sleep problems (insomnia) in adults
- Zolpidem belongs to a class of drugs called sedative-hypnotics. It acts on your brainto produce a calming effect.
- This medication is usually limited to short treatment periods of 1 to 2 weeks or less
- Take this medication by on an empty stomach

Selective GABA Medicines: ZOLPIDEM TARTRATE

- ADRs e.g. pronounced amnesia and more rarely hallucinations, especially when used in large doses
- On rare occasions, these drugs can produce fugue state, wherein patient sleepwalks and may perform relatively complex actions, including cooking meals or driving cars, with no recollection of the events upon awakening
- Memory disturbances
- Daytime withdrawal-related anxiety can also occur from chronic nightly used
- Long-term users increased risk of depression

Drug	Half Life* (h)	Dose†	Comments
Benzodiazepine receptor agonists: Nonbenzodiazepines			
Zaleplon	1	5–20 mg	Ultrashort-acting; can be given for sleep-onset insomnia or after nocturnal awakening (if patients can spend at least 4 h in bed after taking the drug) When given at normal bedtime, least likely to have residual effects
Zolpidem, tablets	2.5	Men: 5–10 mg Women: 5 mg	Effective for sleep-onset insomnia only
Zolpidem oral spray‡	2.7	Men: 5 mg, 10 mg Women: 5 mg	Used for sleep-onset insomnia
Zolpidem, extended-release	2.8	Men: 6.25–12.5 mg Women: 6.25 mg	Effective for sleep-onset insomnia and sleep maintenance insomnia; no tolerance with up to 6 mo of use 3 to 7 nights/wk
Zolpidem, sublingual‡	2.9	At bedtime Men: 5 mg, 10 mg Women: 5 mg Middle of the night Men: 3.5 mg Women: 1.75 mg	More rapid onset of action than zolpidem tablets Higher doses used for sleep-onset insomnia Lower doses used for early awakening (should not be taken unless patients can spend at least 4 h in bed after taking the drug)
Eszopiclone	6	1–3 mg	Effective for sleep-onset insomnia and sleep maintenance insomnia; no tolerance with up to 6 mo nightly use

Others

- **Melatonin**
- **Antihistamines**
- **Antidepressants**
- **Antipsychotics**

Melatonin

- Melatonin, hormone produced in the pineal gland in the brain and secreted in dim light and darkness, among its other functions, promotes sleep in diurnal mammals
- Due to its hypnotic properties, it is available on prescription in many countries and is over-the-counter in others
- A timed-release version, trade name Circadin®, was approved in 2007 in Europe (EU) for use as a treatment for primary insomnia

Melatonin

- Several melatonin receptor agonists that bind to and activate melatonin receptors were developed, include
  - Ramelteon, agomelatine, TIK-301 and tasimelteon
  - Ramelteon (Rozerem®) was approved for treatment of insomnia in the US in 2005
  - In 2009 agomelatine (Valdoxan®, Melitor®, Thymanax®), primarily used for depression, was approved in Europe
  - Both TIK-301 (in 2004) and tasimelteon (Hetlioz®) ten years later were approved in the US for circadian rhythm sleep disorder non-24-hour sleep–wake disorder in totally blind individuals

Sleep-Wake cycle Modifiers

- **How It Works**
  - Stimulates melatonin receptors in the brain area that controls the sleep-wake cycle
- **Duration of Effects**
  - 4-6 hours
- **Side Effects**
  - Headache, drowsiness, dizziness. Uncommonly, problems with sex drive. Loss of menses or problems getting pregnant
- **Dependence Risk**
  - Low

Sleep-Wake cycle Modifiers

- Rozerem(ramelteon)

Melatonin receptor agonists			
Ramelteon	1–5	8 mg	Useful only for sleep-onset insomnia; one of a few hypnotics that are not associated with abuse liability Can be safely given to patients with mild to moderate obstructive sleep apnea or COPD No difficulties with long-term use

Rozerem: RAMELTEON

- This medication is used to treat sleeplessness (insomnia).
- Ramelteon works like a natural substance called melatonin that is produced by your body
  - It helps regulate your sleep-wake cycle (circadian rhythm)

Antihistamines

- Clinically, H_1 antagonists are used to treat certain allergies
- Sedation is a common side-effect, and some H_1 antagonists, such as diphenhydramine (Benadryl) and doxylamine, are also used to treat insomnia.
- Second-generation antihistamines cross the blood–brain barrier to a much lower degree than the first ones, having a much lower sedative effect

Antihistamines:

- **How It Works**
  - Acts on histamine receptors in the brain to cause drowsiness
- **Duration of Effects**
  - 4-6 hours (sleepiness may last longer)
- **Side Effects**
  - Daytime sleepiness; confusion and difficulty urinating in older people
- **Dependence Risk**
  - Low

Antihistamines: Diphenhydramine

- Because of its sedative properties, diphenhydramine is widely used in nonprescription sleep aids for insomnia
- The drug is an ingredient in several products sold as sleep aids, either alone or in combination with other ingredients such as acetaminophen (paracetamol)
- Can cause minor psychological dependence
- Diphenhydramine can cause sedation and has also been used as an anxiolytic

Tricyclic Antidepressants

- Some antidepressants have sedating effects
- Some *may* increase actual quality of sleep (biologically) in contrast to Benzodiazepines that decrease quality
- **Tricyclic Antidepressants**
  - Serotonin antagonists and reuptake inhibitors: Trazodone
  - Tricyclic antidepressants: Amitriptyline, Doxepin, Trimipramine
  - Tetracyclic antidepressants: Mianserin, Mirtazapine

Tricyclic Antidepressants

- Taken in low doses at bedtime (e. g, doxepin 25 to 50 mg, paroxetine 5 to 20 mg, trazodone 50 mg, trimipramine 75 to 200 mg) may improve sleep
- However, antidepressants should be used in these low doses mainly when standard hypnotics are not tolerated or in higher (antidepressant) doses when depression is present
- Ultra low dose doxepin (3 or 6 mg) is indicated for sleep maintenance insomnia

Tricyclic Antidepressants

- Aventyl(nortriptyline)
- Elavil(amitriptyline)
- Pamelor(nortriptyline)
- Sinequan(doxepin)
- Trazodone(desyrel)

Tricyclic Antidepressants

- **How It Works**
  - Binds to multiple brain receptors including acetylcholine; sedating.
- **Duration of Effects**
  - Not well studied
- **Side Effects**
  - Low at usual doses for insomnia. Dizziness, blurry vision, difficulty urinating, cardiac arrhythmias possible. Trazodone can cause prolonged, painful erections.
- **Dependence Risk**
  - Low

Doxepin: Sinequan

- Treatment mental/mood problems such as depression and anxiety. It may help improve mood and feelings of well-being, relieve anxiety and tension, help you sleep better, and increase your energy level
- Usually 1 to 3 times daily, may take up to 3 weeks before get a full effect
- To reduce your risk of side effects (such as drowsiness, dry mouth, dizziness), start this medication at a low dose and gradually increase your dose
- Do not stop taking this medication abruptly. Some conditions may become worse suddenly stopped. Also, withdrawal ADRs such as mood swings, headache, and tiredness.

Nortriptyline: NORTRIPTYLINE HCL

- This medication is used to treat mental/mood problems such as depression. It may help improve mood and feelings of well-being, relieve anxiety and tension, and increase your energy level
- This medication may also be used to help quit smoking.
- Usually 1 to 4 times daily
- To reduce your risk of side effects (such as dry mouth, dizziness), start at a low dose and gradually increase your dose.
- Withdrawal ADRs if drug is suddenly stopped e.g. mood swings, headache, tiredness, and sleep change.
- It may take up to 4 weeks before get the full effect.

AMITRIPTYLINE

- This medication is used to treat mental/mood problems such as depression. It may help improve mood and feelings of well-being, relieve anxiety and tension, help you sleep better, and increase your energy level.
- This medication may also be used to treat nerve pain (such as peripheral neuropathy, postherpetic neuralgia), eating disorder (bulimia), other mental/mood problems (such as anxiety, panic disorder), or to prevent migraine headaches.
- Usually 1 to 4 times daily
- To reduce your risk of side effects (such as drowsiness, dry mouth, dizziness), start at low dose and gradually increase
- Do not stop abruptly, withdrawal ADRs e.g. mood swings, headache, tiredness, and sleep change.
- To see some benefit within a week, it may take up to 4 weeks before get full effect

TRAZODONE

- This medication is used to treat depression. It may help to improve your mood, appetite, and energy level as well as decrease anxiety and insomnia related to depression
- Trazodone works by helping to restore the balance of a certain natural chemical (serotonin) in the brain.
- Usually once or twice daily after a meal or snack
  - If drowsiness is a problem taking 1 dose at bedtime
- To reduce risk of side effects, start at a low dose and gradually increase dose
- Do not stop taking abruptly. Anxiety, agitation, and trouble sleeping can occur if the drug is suddenly stopped
- May take 2 to 4 weeks before get a full effects of the medication

Antipsychotics

- First-generation:
  - Chlorpromazine
- Second-generation:
  - Clozapine
  - Olanzapine
  - Quetiapine
  - Risperidone
  - Zotepine

Miscellaneous others

- Alpha-adrenergic agonist:
  - Clonidine
  - Guanfacine
- Cannabinoids
  - Cannabidiol
  - Tetrahydrocannabinol
- Orexin receptor antagonist
  - Suvorexant
- Gabapentinoids
  - Pregabalin
  - Gabapentin

Orexin Receptor Antagonists

- A serious concern is evidence suggesting nonbenzodiazepine sleeping pills linked to dementia, early mortality, increased risk of cancer; ? dangerous psychiatric drugs.
- Newer class of (potentially safer) sleeping pills under development dubbed the "orexin receptor antagonists."
- "Belsomra" (Suvorexant) approved by the FDA for the treatment of insomnia
- However, remains unknown whether this new class of sleeping pills will be safe over long-term

Orexin Receptor Antagonists: Belsomra (Suvorexant)

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Orexin Receptor Antagonists: Belsomra (Suvorexant)

- Clinically effective intervention for insomnia for up to 4 weeks compared to a placebo
- FDA approval in August 2014 and
- New sleeping pill, relatively expensive
- It remains unknown whether this drug will be preferred over nonbenzodiazepine GABAergic options in regards to long-term safety

Orexin Receptor Antagonists: Belsomra (Suvorexant)

- Recommended dose is 10 mg, taken within 30 min of going to bed, with at least 7 hr before the planned time of awakening.
- Should not to exceed 20 mg once/day
- Most common adverse effect is somnolence

Orexin Receptor Antagonists:

- Other New development Orexin receptor antagonists
  - Lemborexant (E-2006)
  - MIN-202 (JNJ-42847922)
  - SB-649868
  - ACT-462206

TAKE HOME MESSAGE: Tips for treating insomnia

- Cognitive behavior therapy for insomnia (CBT-I) remains the most effective treatment,
- Other nonpharmacologic methods that may be promising include exercise, sleep restriction, meditative movement, and mindfulness based stress reduction
- Among pharmacological treatments, suvorexant blocks orexin receptors, a novel target for reducing wakefulness and enhancing sleep

TAKE HOME MESSAGE: Tips for treating insomnia

- Low-dose doxepin is an antihistamine that has a favorable efficacy and safety profile
- Low-dose zolpidem has been shown to be effective for middle of the night insomnia without the next day sedation of regular zolpidem
- The controversy surrounding the safety of chronic use of sedative hypnotics
  - Drugs should be prescribed with caution, preferably for the short term only