

INSOMNIA

by

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- **Introduction**
- **Bible verse**
- Proverbs 3:24 – When thou liest down, thou shalt not be afraid: yea, thou shalt lie down, and thy sleep shall be sweet.
- **Sleep hygiene**
 - Sleep hygiene includes:
 - regular sleep schedule
 - exercise in late afternoon but not at night
 - removal from bedroom of lights, noise, cold, pets
 - avoid alcohol, caffeine, smoking, daytime naps, staying in bed awake, large meals
- **Insomnia is the inability to sleep. Many drugs have been tried for insomnia:**
 - chloral hydrate in the 1860's
 - bromides in the 1870's
 - paraldehyde in the 1880's
 - barbiturates in the 1930's
 - benzodiazepines in the 1960's and beyond (Dalmane, Restoril, Halcion, ProSom, Doral)
 - zolpidem (Ambien), zaleplon (Sonata), and eszopicolone (Lunesta) in the 1990's
 - ramelteon (Rozerum) in 2005
 - zolpidem extended release (Ambien CR) in 2006 with 7.5 mg released immediately and 5 mg released in two hours
 - ropinirole (Requip) in 2006 and pramipexole (Mirapex) a little later for RLS
 - Circadin, a synthetic melatonin analog approved in Europe 2007
 - Vanda, a beta analog of melatonin is being tested
 - tigabine (Gabitril) is being tested
 - antihistamines, such as diphenhydramine (Benedryl) and doxylamine (Unisom), are sometimes not great sleeping pills since they often lose their effect in seven to ten days; they are used off-label
 - Tylenol PM with diphenhydramine plus acetaminophen is popular as a sleep aide
 - Desyrel (trazadone), Elavil (amitriptyline), Sinequan (doxepin), and Remeron (mirtazepine) have been used off-label for insomnia
 - alcohol, perhaps the number one sleeping agent tried, is a terrible sleeping agent since it disturbs sleep

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- DSMIV R has organized the etiologies of insomnia into five categories:
 - primary insomnia
 - sleep apnea
 - RLS (restless leg syndrome)
 - PLMD (periodic limb movement disorder)
 - insomnia related to another mental disorder
 - MDD (major depressive disorder)
 - bipolar disorder
 - anxiety disorders
 - schizophrenia
 - insomnia related to a general medical condition
 - Alzheimer's disease
 - back pain
 - cancer
 - cardiac disease
 - diabetes mellitus
 - renal disease
 - GI disease
 - GERD
 - HIV
 - menopause
 - nocturia
 - pain
 - Parkinson's disease
 - pulmonary disease
 - thyroid disease
 - insomnia—substance induced
 - albuterol
 - alcohol
 - antidepressants
 - beta blockers
 - caffeine
 - diuretics
 - levodopa
 - oral contraceptives
 - steroids
 - theophylline
 - thyroxine
 - other categories of insomnia
 - circadian rhythm disturbance
 - transient/adjustment insomnia—identifiable stressor
- ***insomnia and diphenhydramine***
 Diphenhydramine (Benadryl, Tylenol PM) is often used OTC for insomnia. At 50 mg it improves sleep in 70%; at greater than 50 mg anticholinergic delirium

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increases (especially in the elderly). Incidentally, Unisom OTC is doxylamine not diphenhydramine.

- ***insomnia, mental disorders, neurochemistry, and neurocircuitry***
 - depression
 - ↑ REM with ↓ REM latency
 - ↓ stage 3 and 4 (delta)
 - ↓ 5HT
 - PTSD
 - ↑ REM with ↓ REM latency, ↑ nightmares
 - ↓ stage 3 and 4 (delta)
 - ↑ locus coeruleus → ↑ NE
 - panic disorder
 - ↑ hyperarousal
 - schizophrenia
 - ↓ melatonin → phase advance sleep syndrome such that one is sleepy in early evening and awakes in early morning
 - ↓ REM
 - ↓ total sleep time
 - ↓ stages 2, 3, and 4 (less stage 4 with ↑ negative symptoms)
 - ↑ restless sleep
 - ↑ stage 2 latency
 - ↑ insomnia precedes relapse
 - ↑ D
 - dementia
 - ↑ restless sleep
 - ↑ HPA axis hyperactivity
 - ↑ cortisol at night
 - Parkinson's disease
 - narcolepsy-like symptoms with nocturia, pain, nightmares, hallucinations, sleep talking, hypersexuality, REM disturbance
 - ↓ total sleep time
 - ↑ restless sleep
 - obstructive sleep apnea and metabolic syndrome
 - activation of HPA axis
 - ↑ leptin → ↑ appetite
 - **Pharmacologic treatments of insomnia include:**
 - GABA alpha-1 subunit drugs with hypnotic effect
 - eszopiclone (Lunesta)
 - zolpidem (Ambien)
 - zaleplon (Sonata)
- Incidentally, alpha-2 subunits as benzodiazepine have anxiolytic effects

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alpha 2 + alpha 3 + alpha 5 = muscle relaxation and alcohol potentiation

- benzodiazepine with alpha and gamma subunits (Dalmane, Restoril, ProSom, Doral)
 - all have GABA_A effects
 - a GABA_B effect
 - a gamma-2 effect
 - any of four alpha subunits (alpha 1, 2, 3, or 5) effects
- melatonin receptor agonist
 - ramelteon (Rozerum)—MT1 and MT2 receptors
 - melatonin
 - Vanda is a beta analog of melatonin. It is in testing.
- antihistamine drugs
 - trazadone (Desyrel)—antidepressant approved
 - Seroquel (quetiapine)—antipsychotic approved
 - Tylenol PM (acetaminophen-diphenhydramine)
 - doxylamine (Unisom)
 - Levoprome (methotrimeprazine)—antipsychotic with antipain effects
 - hydroxazine (Vistaril)—antipain effects
- barbiturate-like drugs
 - chloral hydrate (Somnote)
- other possible GABA acting drugs with antipain effects
 - gabapentin (Neurontin)
 - pregabalin (Lyrica)
- ***sedative-hypnotics: nuances of interest***
 - Medical causes of insomnia include: pain, restless legs syndrome (RLS), hyperthyroidism, COPD, and drugs (alcohol, caffeine, cocaine, amphetamines)
 - The elderly sleep less overall but more in stages 3 and 4
 - Alcohol may induce sleep but causes EMA and decreased quality of sleep
 - H₁ receptor antagonist (diphenhydramine [Benadryl], doxylamine [Unisom]) are OTC drugs used for insomnia; side effects include: daytime sedation, urinary retention, blurred vision, and orthostatic hypotension
 - Melatonin is an OTC pineal gland peptide hormone used off-label in circadian cycle sleep disruption; it may cause daytime sedation and lower body temperature
 - Prescription hypnotic drugs include: the older agents of the 1930's (barbiturates, glutethimide, methaqualone, methyprylone, meprobamate, tybamate, chloral hydrate (Somnote)—these were highly addicting and were very dangerous in overdose); the agents of the 1960's and beyond (flurazepam or Dalmane, tamazepam or Restoril, triazolam or Halcion, estazolam or ProSom, quazepam or Doral); the “Z drugs” of the 1990's and beyond (zolpidem or Ambien, zaleplon or Sonata, eszopiclone or

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Lunesta); and ramelteon (Rozerum) of 2006 that attaches to melatonin receptors.

- The onset of actions varies from fast (Dalmane, Lunesta, Sonata, Ambien) to intermediate (Somnote, Halcion, ProSom, Doral) to slow (Restoril, Rozerum).
- The half-lives varies from long (Dalmane at 30-100 hours, Doral at 25-40 hours, ProSom at 10-24 hours) to intermediate (Somnote at 8-10 hours, Restoril at 9-12 hours) to short (Sonata at 1 hours, Rozerum at 1 to 2.5 hours, Ambien at 1.5 to 4.5 hours, Halcion at 1.5 to 5.5 hours, Lunesta at 6 hours)
- The benzodiazepines are GABA agonists; they work by increasing the frequency of chloride channel openings; barbiturates and alcohol increase the duration of chloride channel opening
- Benzodiazepines change sleep stages; they decrease slow-wave, restorative seep; they decrease REM sleep resulting in decreased memory; discontinuation of benzodiazepines causes REM rebound with increased dreams; benzodiazepines sometimes used as sedative-hypnotics are triazolobenzodiazepine—they include diazepam (Valium), triazolam (Halcion), estazolam (ProSom), alprazolam (Xanax), and midazolam (Versed); they are metabolized by CYP3A4; benzodiazepines in pregnancy have caused cleft plate, delayed ossification, and rudimentary ribs
- Zolpidem (Ambien) is an imidazopyridine; it acts at GABA/A α_1 ; unlike the benzodiazepines, Ambien is absent anxiolytic, anticonvulsant, and myorelaxant effects; it does have the hypnotic effects; it does not alter stages 3 and 4 sleep; it can cause respiratory depression in overdose—flumazenil is used to treat this; selectivity for GABA/A α_1 is lost at higher than standard doses
- Zaleplon (Sonata) is a pyrazolopyrimidine; it acts at GABA/A $\alpha_1 \alpha_2 \alpha_3$; it is metabolized by aldehyde oxidase
- Eszopiclone (Lunesta) is a cyclopyrrolone; eszopiclone has less memory problems than benzodiazepines; it alters sleep stages little—stage 2 and slow-wave do increase but REM is unchanged; it does not cause respiratory depression; it does not cause rebound insomnia
- Ramelteon attaches to MT1 and MT2 melatonin receptors; it does not change sleep architecture
- The most frequent used off-label sleep aide in the U.S. is trazadone (Desyrel); trazadone is an antidepressant; it is a triazolopyridine; trazadone increases slow-wave sleep; it does not usually alter REM sleep; its half-life is 6-9 hours; side effects of trazadone include priapism (1 in 10,000 to 40,000 cases), constipation, and hypotension
- TCAs (amitriptyline, doxepin) are used off-label for insomnia; they also decrease pain; they inhibit REM sleep and thus, are associated with REM rebound

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- Mirtazapine (Remeron), an antidepressant, is used off-label for insomnia
- Hydroxyzine hydrochloride (Vistaril, Atarax) is used off-label for insomnia; it is an H₁ receptor antagonist; it can cause hypotension. Vistaril is often not used with lithium, Phenobarbital, aminophylline, cefloramphenicol, and penicillin.
- Barbiturates, butabarbital, Phenobarbital, and secobarbital are used for insomnia, but they are very addicting and cause respiratory depression; abrupt discontinuation of barbiturates can potentially result in fatal withdrawal reactions
- Restless legs syndrome (RLS) causes insomnia in many people; Requip and Mirapex are approved for RLS; Klonopin is used off-label as is Neurontin
- Triazolam (Halcion) has been known to cause anterograde amnesia
- The drugs (Ambien, Sonata, Lunesta) are biotransformed by several CYP enzymes and therefore, drug interactions may be less; carbamazepine and erythromycin do increase plasma zopiclone and rifampin decreases zopiclone; cimetidine increases Sonata since it inhibits aldehyde oxidase and CYP3A4 that metabolizes zaleplon (Sonata), cimetidine increases zaleplon by 85%; ketoconazole and erythromycin also increase plasma zaleplon; rifampin decrease zaleplon
- Vanda, a beta analog of melatonin, is being tested as a sleep medication
- Circadin, a synthetic melatonin analog in Europe
- Benzodiazepines (Dalmane, Restoril, Halcion, ProSam, Doral) were the main treatments for insomnia prior to the 1990's. They bind to GABA_A. GABA_A consists of five subunits formed from 19 different subunits from seven subunit families (α , β , γ , δ , ϵ , θ , ρ). This diversity of subunits allows for many different subunit GABA_A receptors. The α subtypes (α_{1-6}) are in the brain areas involved in sleep, sedation, and memory. The GABA_A α_2 , α_3 , are involved in anxiolytic, anticonvulsant, cognitive, and psychomotor activity. Since the benzodiazepines act at multiple GABA_A receptor subtypes side effects are increased. In contrast, non-benzodiazepines of the 1990's and beyond (Ambien, Sonata, Lunesta) are more specific (mostly GABA α_1) in how they work.
- **Conclusion**
 - Bible verse
 - Proverbs 3:24 – When thou liest down, thou shalt not be afraid: yea, thou shalt lie down, and thy sleep shall be sweet.

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