Managing Insomnia

With acknowledgement of the work of Dr A Fernando, Sleep Specialist, Department of Psychological Medicine, University of Auckland

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Some people who found me useful

- HVDHB Acute Inpatient Psychiatry Unit
- HVDHB Community Mental Health

Also;

- NZHPA PsychSIG
- Eli Lilly & Co
- Whitireia Polytechnic School of Nursing
- Epilepsy NZ
- PHARMAC
- GP CME Christchurch August 2010
- Kowhai Health PHO
- Various practitioners in the Hutt Valley and NZ

What is Normal?

The adult human requires about 7-9 hours of sleep daily.

Daily sleep tendency peaks at two times;

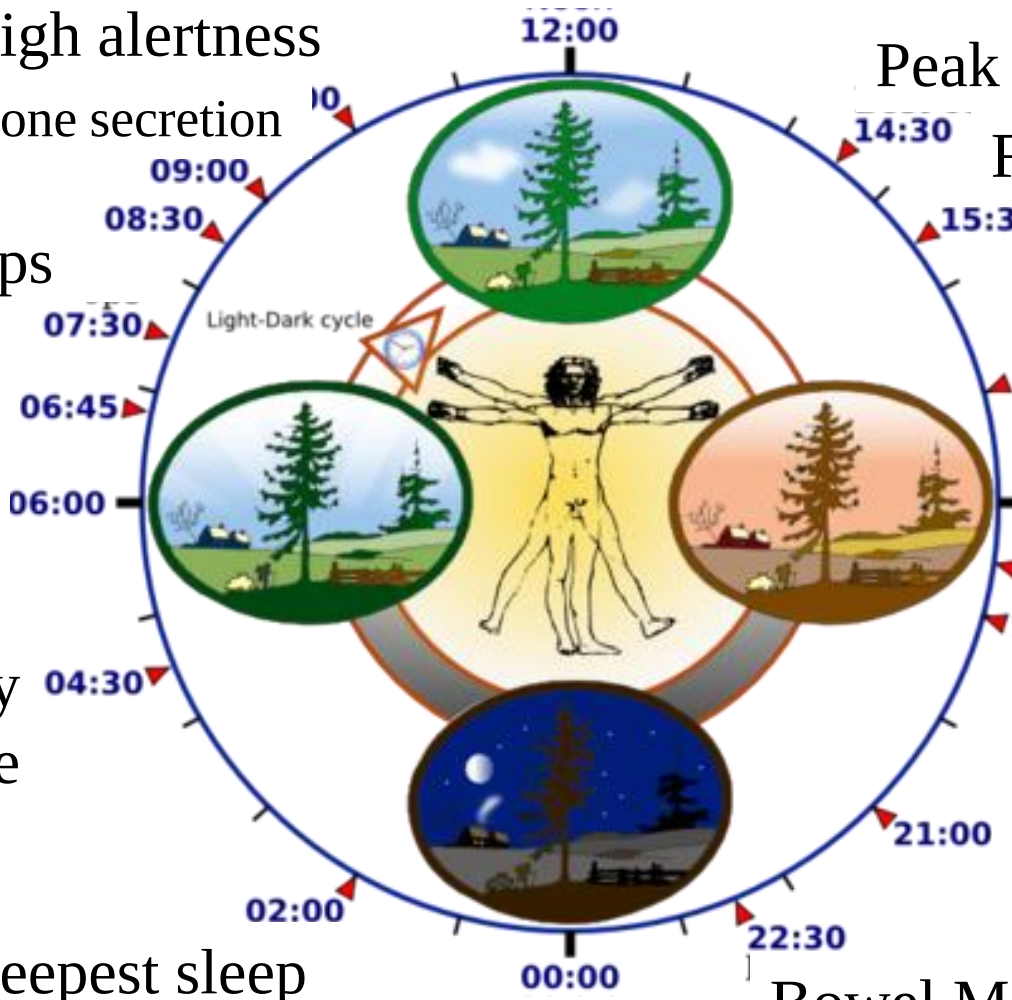
1. Nocturnal bedtime
2. Midafternoon, the siesta hour, 12 hours after middle of the nocturnal sleep period, (not assoc. with lunch).

Practical application;

- Napping can be troublesome if one needs to be alert.
- Advantageous for elderly with daytime sleepiness but too long daytime napping can disturb getting to sleep at night.
- The jet-lagged traveller.

Zulley 1985, Czeisler 1982, Gillin & Ancoli-Israel 2005

The Human Biological Clock



High alertness

Highest testosterone secretion

Melatonin stops

Sharpest rise in BP

Lowest body temperature

Deepest sleep

Midnight

Bowel Movements Suppressed

Melatonin secretion

Highest body temperature

Highest BP

Muscle strength

Peak CV efficacy &

Fastest reaction time

Peak co-ordination

What keeps the biological clock ticking?

Zeitgebers

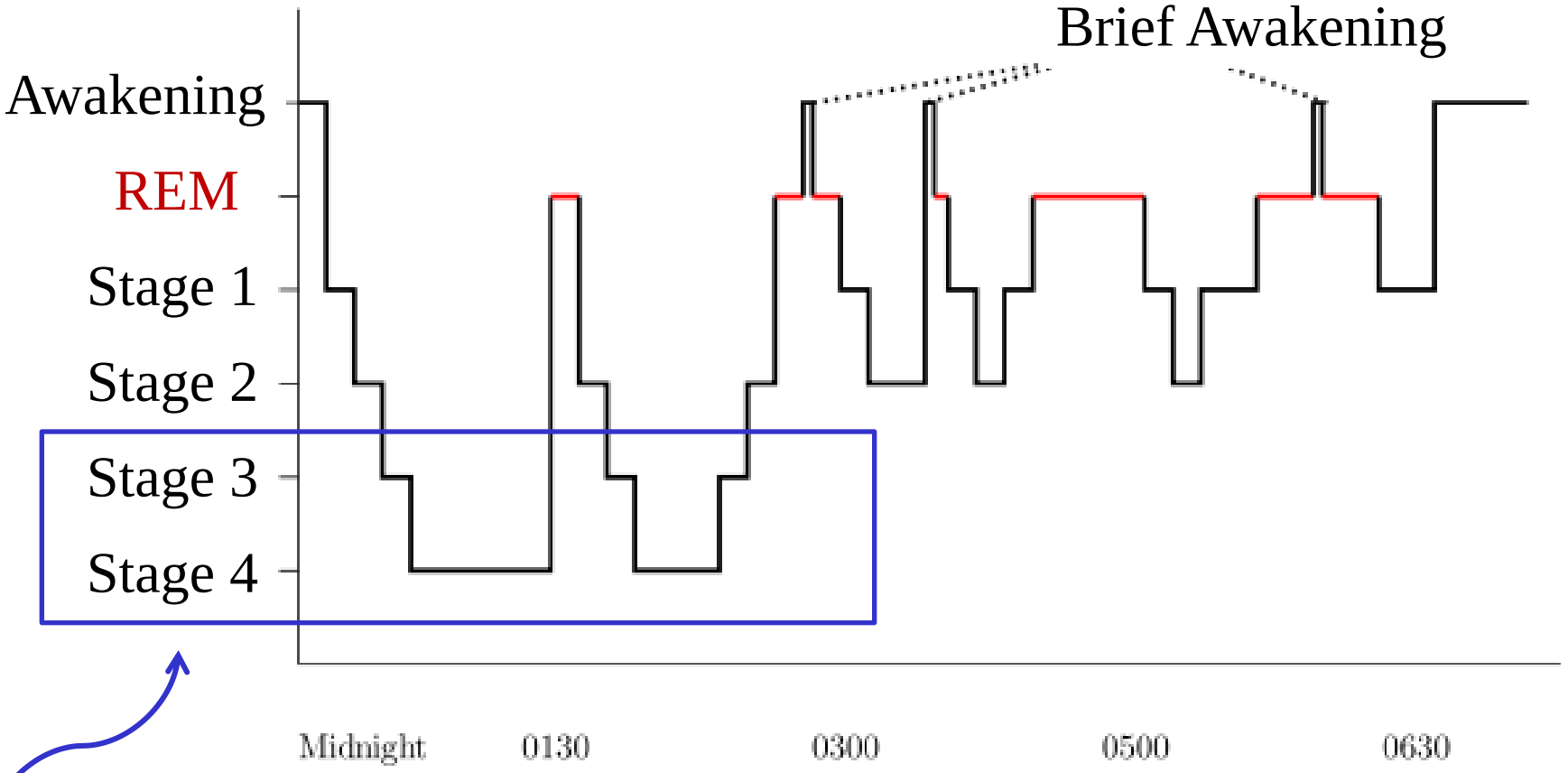
Aschoff J (1965) The phase-angle difference in circadian periodicity. In "Circadian Clocks" (J. Aschoff, ed.). North Holland Press, Amsterdam

Zeitgebers (*time-givers or synchronisers*)

- The strongest zeitgeber for both plants and animals is light, also; temperature, social interactions, pharmacological intervention, exercise, eating and drinking patterns.

- In the absence of zeitgebers, or cues about the time of day, humans self-select a sleep-wake cycle of 24.5 to 25 hours.
- Thus shifts in the cycle of rest and activity are easier when the cycle is lengthened rather than shortened.
  - In travelling west rather than east, or
  - Rotating from afternoon to evening shift rather than afternoon to morning shift.
- Practical application; the shift worker with sleep difficulty.

Hypnogram



2004 the American Academy of Sleep Medicine combined stages 3 & 4; now called stage 3, delta- or slow-wave sleep

Non-REM Sleep

N1	Lose some muscle tone and most conscious awareness of the external environment. May get sudden twitches and hypnic jerks, with the onset of sleep. May also experience hypnagogic hallucinations during this stage.
N2	Muscular activity decreases, and conscious awareness of the external environment disappears. This stage occupies 45–55% of total sleep in adults.
N3	Parasomnias such as night terrors, nocturnal enuresis, sleepwalking, and somniloquy occur in this stage.

REM Sleep

- Most vividly recalled dreams occur during REM sleep.
- A descending muscular atonia is seen.
- Muscle paralysis may be necessary to protect against self-damage through physically acting out scenes from the often-vivid dreams that occur during this stage.
- Typically 4-5 periods of REM occupy 20–25% of total sleep in adults, about 90–120 minutes of a night‘s sleep.
- Quite short periods earlier in sleep, longer toward the end.
- In REM the activity of brain neurons is quite similar to that during waking hours; thus, the REM-sleep stage is also called paradoxical sleep.

REM Sleep Behaviour Disorder (RBD)

- Arises from REM sleep, may be recalled and described.
  - Lack of atonia in REM sleep, and
  - Increased vivid or unpleasant content of dreams;
  - Acting out of dreams due to lack of muscle paralysis in REM
- Incidence unknown, occurs in older people, increases >55
- Markedly male preponderance
- Possibly idiopathic but mostly associated with;
  - Parkinson's disease , up to 50%
  - Lewy body dementia, up to 70%
  - Multiple system atrophy, more than 90%

Gagnon JF, Postuma RB and Montplaisir J (2006) Update on the pharmacology of REM sleep behaviour disorder. Neurology 67:742–747.

Relative to Younger People, Older Adults Report

- Stages 1 & 2 sleep tend to increase
- Stages 3 & 4 sleep tend to decrease
- Percentage of REM does not change appreciably.
- More frequent night-time awakenings, may not be recalled.
- Early morning awakening.
- Sleep tends to be shallow, fragmented and variable in duration in middle-aged and elderly adults.
- Daytime sleepiness increases, over 80% older adults nap.
  - Much of this is secondary breakdown of circadian rhythm, leads to advancement and decline in amplitude.
  - May achieve same total sleep time each day.
- Wakefulness After Sleep Onset (WASO) usually increases.

Relative to Younger People, Older Adults report

- Less exposure to bright light, more blindness.
- Most sleep disturbance is due to medical burden rather than to aging itself.
- Greater use of sedative-hypnotic medication.
- However, over time sleep complaints do not increase in older people.
- Many older people have lowered expectations with advancing age:
  - “I am old therefore I’m more sleepy during the day”
  - Can lead to poor reporting.

Gillin c, Ancoli-Israel S. The Impact of Age on Sleep and Sleep Disorders. In;Salzman C, Editor. Clinical Geriatric Psychopharmacology 4th Edition (2005) Lippincott, Williams & Wilkins.

Sleep Hygiene

- Increase daily exercise, not in the evening
- Reduce or stop daytime napping
- Reduce caffeine or alcohol intake, especially before bed
  - Avoid caffeine after midday
- Stop smoking
- Use the bed only for sleeping and sex
- Use anxiety management or relaxation techniques
  - Preparation for sleep
- Develop a regular routine or rising and retiring
  - At the same times each day
  - Regardless of the amount of sleep taken

Facts about Sleep & Tiredness in USA

- 39% of adults sleep less than 7 hours on weeknights
- 36% of people >15 report insomnia at least occasionally
- 54% of people >55 report insomnia once a week or more
- Average number of fatal crashes caused by drowsy driving each year: 1,550
- 39% of health care workers who have had a near miss accident at work because of fatigue in the last year
- 19% of health workers who report worsening a patient's condition because of fatigue
- 44% of law enforcement workers who report having taken unnecessary risks while tired
- 80% of US regional pilots sometimes nod off in cockpit

I Can't Sleep, Arlene Weintraub, Business Week Issue 3867, 1/26/2004,

One Expert Perspective

"Many patients with sleep problems fail to receive treatment because the sleep screening process is far too time-consuming for the average physician to administer during a brief office visit"

Therefore, the standard approach to treatment is;

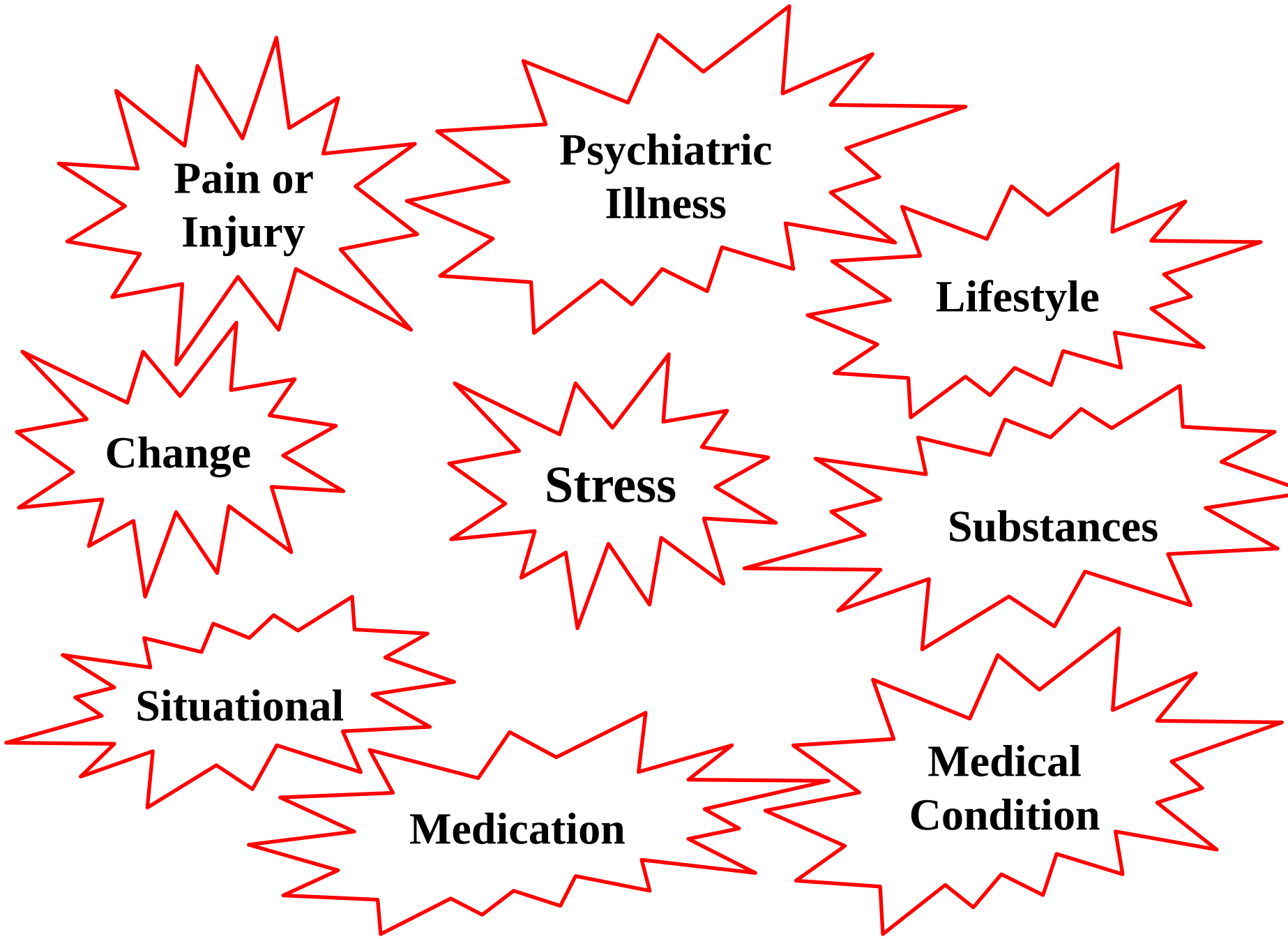
- Here, take this pill.
- Change your lifestyle; diet, exercise, stress reduction, more vacation time.

Dr. Thomas Roth, Henry Ford Medical Centers

When a patient presents
with a sleep symptom,

The most important question
before anything else;

What is causing the sleep symptom?


Pain or Injury
Psychiatric Illness
Lifestyle
Change
Stress
Substances
Situational
Medication
Medical Condition

Or, maybe there is a primary sleep disorder.

Gringras G, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders.
J Psychopharmacol published online 2 September 2010.
http://jop.sagepub.com/content/early/2010/08/31/0269881110379307

How long has this been going on?

- Transient or short-term insomnias usually occur in persons under stress; jet-lag, admission to hospital, acute pain.
- Chronic symptomatology, lasting four weeks or more, frequently associated with;
    - Psychiatric conditions
    - Medical disorders
    - Abuse of alcohol or sedatives
    - Iatrogenic effects of drugs or substances
    - Disturbances of sleep-wake cycle
    - Sleep apnoea
    - Periodic limb movements during sleep (PLMS)

Evaluation of Chronic Sleep Complaints

- History and review of complaint
  - Predisposing, precipitating, perpetuating factors
- Review of difficulties falling asleep
- Timing of sleep and wakefulness
- Evidence of excessive daytime sleepiness and fatigue
- Bedtime routines; setting, anxiety, fears, enuresis
- Medical & neurological examination
- Use of prescription medicines and non-prescription drugs
- Evidence of breathing disorders
- Abnormal movements; myoclonus, cramps, cold feet
- Psychiatric history
- Social & occupational history

Evaluation of Chronic Sleep Complaints

- Sleep diary for two weeks
- Interview bed partners or persons who would observe
- Tape recording of respiratory sounds?
- Review of daily activities and physical environment;
  - Mealtimes, light-dark exposure, emotional and physical stimulation, ambient temperature, noise levels

Prticularly for the Elderly

- Cognition, orientation, confusion
- Ability to take care of activities of daily living
- Acute and chronic physical disorders
- Nocturia, enuresis, incontinence
- Vision and hearing
- Gait and mobility
- Orthopnoea, paroxysmal nocturnal dyspnoea
- Congestive heart failure
- Arthritis and painful conditions
- Depression, anxiety, bereavement
- Night wandering

Good Questions for Older Adult:

- Rather than “do you nap?”
  - “Do you find yourself falling asleep when you don’t want to; for example; while driving, while talking with friend and family, or watching an interesting television program?”
  - “Do you need to nap often in order to function well?”

Major Groups of Symptoms

Insomnia

- Poor unrefreshing sleep
- Initial middle late insomnia = delay or fragmentation
- Daytime consequences

Excessive daytime sleepiness

- Difficulty maintaining desired wakefulness
- Falling asleep inappropriately
- Excessive amount of sleep, hypersomnia

Parasomnias

- undesirable physical or experiential events during sleep

Also Presenting as Insomnia

- Psychiatric disorders; 50% cases of depression or anxiety.
- Medical problems:

Chronic pain	Hyperthyroidism
Chronic fatigue syndrome	Fibromyalgia
Myalgic encephalopathy	GORD

- Medications
- Substance use
- Circadian rhythm disorders; DSPD, jet lag, shift worker
- Poor sleep hygiene
- Primary insomnia
- Other sleep disorder; OSAS, RLS, parasomnias, nocturnal panic, nightmares

Great Tools:

- Sleep Diary for two to four weeks;
  - May not be the best record but good enough,
  - Most people recall worst experiences not successes,
  - Can help patient appreciate successes,
  - Source of concern for the anxious, fretful or obsessive.

- Sleep questionnaire;

  Arroll B, Fernando A. Falloon, K. 10-Minute Consultation: Sleep Disorder (Insomnia). British Medical Journal 2004;337

  www.insomniaspecialist.com

Evaluation of Insomnia

- Initial, middle or late insomnia?
- Effects on next day, any safety concerns – driving, etc?
- Triggers, onset, course, duration?
- Sleep schedule;
  - usual bedtime, awakenings, final waking time?
- Daytime routines;
  - meals, exercise, relaxation, computer, naps?
- Sleep conditions?
- Current and past treatments for insomnia?
- Medicines or Substances; caffeine, nicotine, EtOH, other?
- Other symptoms
- History; Psychiatric, Medical, Family sleep symptoms?

Treatment of Insomnia

- Find the cause and treat that.
- Sleep hygiene, chronic insomniacs have usually looked at.
  - Treat bedroom like a cave, have pre-sleep routine, etc.
  - Check compliance with sleep hygiene.
- Cognitive Behavioural Treatment for insomnia
  - Sleep rescheduling, effective in 70-80%
  - www.cbtforinsomnia.com
- Decreasing arousal with mind training techniques
  - www.calm.auckland.ac.nz

- Hypnotics may have a role for some, but are not the primary treatment for chronic insomnia.

Conditions Presenting as EDS

- Sleep deprivation
- Sleep apnoea, very commonly associated
- Narcolepsy, incidence around 1:10,000
- Idiopathic hypersomnia
- Medications and substances
- Circadian rhythm disorders can look like excessive sleepiness
- RLS, PLMS, Parasomnias
- Depression
  - SSRI may **cause** fatigue in a small number of patients, usually the dose gets increased, but decrease and wait could be better, do not need to stop the SSRI.
- Neurologic conditions

Evaluation of EDS

- Sleepiness vs fatigue
- Frequency, duration, times of the day?
- Any safety concerns – driving, etc?
- Amount and quality of sleep at night?
- Sleep symptoms; OSAS, RLS, circadian, parasomnias?
- Medicines or Substances; caffeine, nicotine, EtOH, other?

- Collateral information, from bed partner or caregiver.
- Epworth Sleepinees Scale; >10 EDS, <1 insomniac.
- Overnight sleep study

Treatment for EDS

- Find the cause and treat that.

- Sleep apnoea
  - CPAP is the gold standard
  - Surgery?
  - Weight loss?

- Idiopathic hypersomnia
  - Stimulants; dexamphetamine, methylphenidate
  - Modafinil; not subsidised in NZ, specialist.

Parasomnias

- NREM;
  - Sleep walking (safety risk), sleep talking (becomes a problem when severe), confusional arousals, sexual behaviours.
- REM;
  - Nightmare disorder (often associated with PTSD, depression or anxiety), REM Behavioural Disorder, sleep paralysis.
- Others;
  - Sleep related dissociative disorder, sleep enuresis, sleep related eating disorder.

Treatment of Parasomnias

- Find the cause.
- Priorities are to;
  - Minimize possible trigger factors such as frightening films, caffeine, alcohol or meals late at night, and
  - To make sure there is a stable and adequate sleep–wake schedule
- Sleep walkers, sleep talkers;
  - Decrease stress and reduce alcohol
- Safeguard against harm to the patient, such as by locking windows, bolting doors, or sleeping on the ground floor, and safety of the bed partner or nearby children also requires attention.
- Low-dose hypnotics may be very effective for some.

Psychiatric Disorders & Sleep

- Primary insomnia
- Mood disorders
- Anxiety disorders
- Psychotic disorders
- Substance use
- Eating disorders
- Other cognitive disorders
- Borderline personality disorders

Primary Insomnia

- Around 30% of chronic insomniacs
- May be a marker for future depression

- Initial, middle or late insomnia,
- Not attributable to other sleep, psychiatric or medical disorders,
- Poor functioning the next day,
- Hyperarousal, tired but wired.

Treatments for Primary Insomnia

- CBT for insomnia:
  - Address distorted cognitions about sleep and insomnia
  - Sleep hygiene
  - Stimulus control
  - Sleep restriction, sleep rescheduling

- Non-medication:
  - Relaxation techniques
  - Meditation, especially mindfulness of breathing
  - Cardiovascular exercise, especially in the mornings
  - Light treatment, sun or bright light in mornings

Treatments for Primary Insomnia

- Medication:
  - Z-drugs preferably, or benzodiazepines
  - Sedating antidepressants, antihistamines, antipsychotics

- Melatonin not effective, no good evidence, yet some patients do well in defiance of the literature
- Valerian not recommended, interactions, sensitivities.

Mood Disorders: Depression

- Insomnia in 60-80% of depressions
- Hypersomnia in 15-20% of depressions
- On polysomnogram in depression;
  - Sleep disruption; initial, middle, late
  - REM sleep onset is earlier
  - SWS, the deep refreshing sleep, is reduced

- Insomnia can be an early sign of depression
- If depression resolves but insomnia does not then likely to relapse.

Mood Disorders: Bipolar

- In bipolar depression may get ‘hungry’ for sleep
  - Increased total sleep time, Hypersomnia
  - Excessive daytime sleepiness

- In mania
  - Lack of sleep may precipitate or be the first sign of mania
  - Decrease in total sleep time
  - If asked, may state that sleep is wonderful

In Anxiety Disorders

- Longer sleep latency (initial insomnia)
  - Ruminate, very busy worrying
- Sleep disruption, fragmentation (middle insomnia)
- Decreased total sleep time
- Nocturnal panic
  - Stage 2-3 sleep
- Nightmares common in some groups;
  - PTSD
  - Occurs during REM sleep

Subsyndromal Anxiety Disorders

- Perfectionists
- Ruminatives
- Mind chatterers

In Schizophrenia

- More variable patterns
- Longer sleep latency (initial insomnia)
  - Ruminate, very busy with intrusive thoughts, voices
- Sleep disruption, fragmentation (middle insomnia)
- Decreased total sleep time
- Sleep apnoea
- Circadian shifts, even to the point of sleep/wake reversal.

Causes of Sleep Symptoms: Substances

- Caffeine,
  - adenosine receptor blocker,
  - stimulant and diuretic,
  - 4-7hour half-life and effects can last up to 14 hours
- Nicotine,
  - Delays sleep onset
  - Alerting effects
- Stimulants,
  - Amphetamines, cocaine, methylphenidate
- Ginseng
- Withdrawal from alcohol or drugs

Causes of Sleep Symptoms: Alcohol

- Shortens sleep latency (switches off alertness)
- As this effect wears off;
  - Sleep becomes shallow and fragmented
  - Disrupts REM sleep
  - Increased vivid dreaming and nightmares
  - Tachycardia, sweating.
- Increased snoring
- Increased nocturnal awakenings, possibly diuretic effect
- Increased apnoeic episodes
- Increased leg movements
- Chronic users, particularly when hospitalised may experience withdrawal symptoms

Causes of Sleep Symptoms: Cannabis

- Decreased sleep onset latency
- Increase in slow wave sleep which may decrease with chronic administration
- Decrease in total REM sleep and REM sleep density
- Possibly contributory to increased irritability in users

Adverse effects on sleep during withdrawal period:

- Sleep onset latency
- Total SWS reduction
- Increase in REM sleep time over first week without, which has been correlated with an increase in strange dreams

What Else is Causing the Sleep Symptom?

- Age related
- Menopause
- Medical condition
  - Pain, GORD, Hyperthyroidism, Fibromyalgia, Chronic Fatigue Syndrome/Myalgic Encephalopathy, Sleep apnoea, Bruxism, Social causes, Restless legs Menopause, Seizures, Epilepsy.....

Epilepsy and Sleep

- Disruption and lability of REM sleep
- Reduced percentage of sleep time spent in REM sleep
- Increased wake after sleep onset
- Prolonged onset of sleep or REM sleep
- Increased number of arousals, awakenings, and stage shifts.
- Holds true even with the absence of seizures
- Observed in patients with idiopathic generalized epilepsy and temporal lobe epilepsy, although more so in the latter.
- Sleep organization appears to be more disrupted in temporal lobe epilepsy than frontal lobe epilepsies.

Medication

Causes of Sleep Symptoms: Medication

- Adrenaline
- Amphetamines
- Anticholinergics
- Anticonvulsants
- Antipsychotics
- Beta agonists, beta blockers
- Bupropion
- Cimetidine
- Clonidine
- Corticosteroids
- Daunorubicin
- Diuretics
- Interferon
- Levodopa
- Long-term hypnotic
- Medroxyprogesterone
- Methyldopa
- Methylphenidate
- Monoamine oxidase inhibitor
- Oestrogen
- Oral contraceptives
- Phenytoin
- Pseudoephedrine
- SSRI
- Theophylline/aminophylline
- Thyroxine, levothyroxine
- Triiodothyronine
- Venlafaxine

Common Drugs That May Cause Insomnia

- Corticosteroids: Prednisone in doses of 20mg or more
- Stimulants; amphetamine, methylphenidate, caffeine.
- Drugs of abuse; methamphetamine, cocaine, party pills.
- Sympathomimetics
- Adrenaline, ephedrine, pseudoephedrine.
- Thyroxine, levothyroxine, triiodothyronine.
- Aminophylline, theophylline.
- Levodopa
- Estrogen
- Anticonvulsants
- SSRI

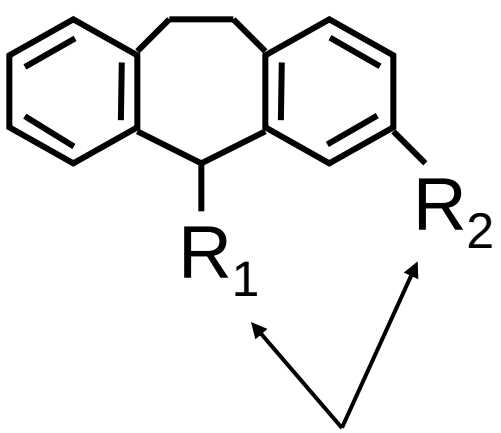
Antidepressants & Sleep

Drug	Relevant mechanism	Effect on sleep
Sedating Tricyclics	H_1 antagonist, $alpha_1$ antagonist M_1 antagonist	Shorten sleep latency Increase total sleep time Increase Short Wave Sleep Suppress REM sleep
Activating Tricyclics: Desipramine protryptiline	NA reuptake inhibition	Increase sleep latency Increase awakenings Decrease total sleep time Activating
SSRI	5HT reuptake inhibition	Increase sleep latency Decrease sleep continuity Increased awakenings Decreased total sleep time REM suppression

Tricyclic Antidepressants, TCA

- Amitriptyline
- Clomipramine
- Desipramine
- Dothiepin
- Doxepin
- Imipramine
- Nortriptyline
- Trimipramine

Basic tricyclic structure



Variable groups

Activity of Tricyclic Antidepressants

Antidepressant effect:

Serotonin reuptake inhibition

Noradrenalin reuptake inhibition

Adverse effects:

Alpha adrenergic A1 & A2 antagonism

Histamine H1 & H2 receptor blockade

Acetylcholine (Muscarinic) receptor blockade

Sodium Channel Blockade

Produces quinidine like effect on cardiac conduction:
10-14 days supply may be fatal in overdose.

Adverse Effects of Tricyclic Antidepressants

- Arrythmias, heart block
- Postural hypotension, syncope
- Antimuscarinic effects
- Sedation
- Tremors, dyskinesia
- Sexual dysfunction
- Blood dyscrasias
- Behavioural disturbances
- Convulsions
- Endocrine adverse effects
- Increased appetite, weight gain

Fatal in Overdose

Orthostatic hypotension
CNS changes
Blurred vision
Dry mouth
Constipation
Urinary retention
Sedation
Sleep disturbance
Reduced sweating

Galactorrhea
Gynaecomastia

Shades of Difference

More sedative:

- Amitriptyline
- Clomipramine
- Dothiepin
- Doxepin
- Trimipramine

More marked anticholinergic effects:

⦸ Amitriptyline

⦸ Imipramine

Greater cardiac risk:

⦸ Amitriptyline

⦸ Imipramine

Stimulant activity:

⦸ Protriptyline

More serotonergic, 3^0 amines:

Clomipramine

Amitriptyline, Imipramine

More noradrenergic 2^0 amines :

Desipramine

Nortriptyline

BPAC NZ Recommends Nortriptyline

If a tricyclic is indicated, nortriptyline is preferable to other tricyclics as it has less risk of adverse effects;

- Is less sedating
- Less likely to cause hypotension
- Less likely to cause anticholinergic effects

Than other tricyclics such as amitriptyline, dothiepine and doxepin.

BPJ 14, June 2009

Antidepressants & Sleep

Drug	Relevant mechanism	Effect on sleep
Bupropion	DA & NA reuptake inhibition	Increase sleep efficiency Decreased REM latency Increased REM sleep time Activating for some people
Venlafaxine	5HT & NA reuptake inhibition	Increase awakenings Decrease stage 2-3 REM suppression PLMS Not known to improve sleep
Mirtazepine	5HT2, 5HT3, H1, antagonist	Decrease sleep latency Increased total sleep time LOW doses more sedating: 7.5 to 15mg

Antipsychotics & Sleep

Drug	Relevant Mechanism	Effect on sleep
Olanzapine	5HT2 antagonism H1 antagonism	Increase sleep continuity Increased Short Wave Sleep Low doses 1.25-5mg
Quetiapine	5HT2 antagonism H1 antagonism	Increased sleep continuity Increased total sleep time Low doses 6.25-50mg

Benzodiazepines: First Things - Gamma-Amino Butyric Acid, GABA

- GABA is an inhibitory neurotransmitter,
- GABA activity is widespread in the brain,
- GABA-A receptor activity hyperpolarises neurons making them less responsive.

- GABA is a safety mechanism for the very excitable human brain, although, the excessive stimulation of GABA produced by exogenous chemicals like benzodiazepines, makes GABA more of a dimmer switch.

What Benzodiazepines do with GABA

- All benzodiazepines interact with a booster site on the GABA-A receptor to enhance the inhibitory effect of GABA, the ongoing nerve impulse may be completely blocked.
- Consequently, brain output of excitatory neurotransmitters is reduced; acetylcholine, dopamine, noradrenaline, serotonin.
- These are responsible for normal alertness, memory, muscle tone and coordination, emotional responses, endocrine gland secretions, heart rate and blood pressure, and a host of other functions, all of which may be impaired by benzodiazepines, and this could be more pronounced with long-term therapy.

Pharmacological Actions & Clinical Uses of Benzodiazepines

Action	Clinical Uses
Hypnotic	Short-term treatment of insomnia.
Anxiolytic	Short-term or intermittent treatment of some anxiety disorders. Short-term aid to alcohol/other CNS depressant drug withdrawal.
Anticonvulsant	Status epilepticus. Drug-induced convulsions. Short-term or adjuvant treatment of some types of epilepsy.
Amnesic	Premedication before surgery. Minor surgical procedures.
Myorelaxant	Painful muscle spasms. Some dystonias and involuntary movements.

Prof. C H Ashton, Psychiatric Annals Volume 25: pp158-165 March 1995

Benzodiazepines Gain Favour

- Late 1970's; Most commonly prescribed drugs in the world.
- 1 in 5 women and 1 in 10 men in Europe took them at some time each year.
- Prescribed long-term, often for many years,
- Prescribed for anxiety, depression, insomnia and ordinary life stresses.

Benzodiazepines Lose Favour

- Early 1980's; in England long-term prescribed users realised
- The drugs tended to lose their efficacy over time, and
- Became associated with adverse effects.
- Patients found it difficult to stop because of withdrawal effects
- Many complained that they had become addicted,
- Throughout the 1980s there was a public outcry against benzodiazepines in the U.K. resulting in widespread media coverage in the press, radio and television and a burgeoning of self-help groups and withdrawal clinics.

What Long-Term Benzodiazepine Patients Find

1. They have taken benzodiazepines in prescribed therapeutic doses for months or years, usually low doses.
2. They have gradually come to need benzodiazepines to carry out normal, day-to-day activities.
3. They have continued to take benzodiazepines although the original indication for prescription has disappeared.
4. They have difficulty in stopping the drug, or reducing dosage, because of withdrawal symptoms.
5. If on short-acting benzodiazepines they develop anxiety symptoms between doses, or get craving for the next dose.

What Long-Term Benzodiazepine Patients Find

6. They contact their doctor regularly to obtain repeat prescriptions.
7. They become anxious if the next prescription is not readily available.
8. They may carry their tablets around with them and may take an extra dose before an anticipated stressful event or a night in a strange bed.
9. They may have increased the dosage since the original prescription.
10. They may have anxiety symptoms, panics, agoraphobia, insomnia, depression and increasing physical symptoms despite continuing to take benzodiazepines.

Use of benzodiazepines should not exceed two to four weeks

- Canada 1982 – Health Canada, continuous use of benzodiazepines should not exceed 2 weeks.
- United Kingdom 1988 – Committee on Safety of Medicines, bulletin to all doctors; Benzodiazepines are indicated for the short-term relief, 2-4 weeks only, of anxiety or insomnia that is severe, disabling or subjecting the individual to unacceptable distress. Benzodiazepines can cause or exacerbate depression and increase the risk of suicide.
- New Zealand 1989 – Department of Health, short-term treatment with benzodiazepines may be beneficial but use for more than 4 weeks could well be harmful.

And still should not exceed four weeks

- United Kingdom 1999 – Department of Health – repeated same message.
- Ireland 2002 – Report of the Benzodiazepine Committee, benzodiazepines should not be prescribed for more than 1 month for anxiety or more than 2-4 weeks for insomnia.
- Denmark 2003 – National Board of Health, prescription of benzodiazepines should be restricted to a maximum of 2 weeks as sleeping pills or 4 weeks as anxiolytics.
- United Kingdom 2004 – Chief Medical Officer, Department of Health – same message.

- United States to present: FDA approved use of sedative/hypnotics is no longer than 35 days, with the exception of eszopiclone only.

Current Committee on Safe Use of Medicines Advice, BNF 61

1. Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness.
2. The use of benzodiazepines to treat short-term or mild anxiety is inappropriate and unsuitable.
3. Benzodiazepines should be used to treat insomnia only when it is severe, disabling, or subjecting the individual to extreme distress.

Benzodiazepine Problems

- Dependence estimated in up to half of long-term users.
- Rebound & withdrawal in up to 80% when discontinue after 4months or more.
- 10-15% chronic users withdrawal is highly difficult.
- Tolerance develops to sedative effect in weeks to months.
- Tolerance develops to anxiolytic effect in months
- Shown to decrease psychomotor ability, visual speed, perception, information processing, verbal learning, concentration, cognition, motivation, attention, co-ordination and reaction time.
- Episodic memory may also be impaired, which can lead to memory lapses or blackouts.
- Paradoxical stimulant effects

- Benzodiazepines have consistently been implicated in the risk of falls, which can lead to significant morbidity and health costs, particularly in the elderly.
- A number of studies have found that patients taking benzodiazepines are at a significantly increased risk of involvement in a road traffic accident — the risk seems greatest early in treatment but persists beyond this time.

Pharmacokinetic Comparison

Elimination Half-life and Approximate Dosage Equivalents	Half-life (/hrs) (active metabolite)	Approximately Equivalent to 10 mg Diazepam
Alprazolam	6-12	0.5 mg
Diazepam	20-100 (36-200)	10 mg
Lorazepam	10-20	1 mg
Oxazepam	4-15	20 mg
Loprazolam	6-12	1 mg
Lormetazepam	10-12	1 mg
Nitrazepam	15-38	10 mg
Temazepam	8-22	20 mg
Triazolam (withdrawn in UK 1991)	2-3	0.5 mg

Prof. C H Ashton, Psychiatric Annals Volume 25: pp158-165 March 1995

Adverse Effects of Benzodiazepines

- Oversedation → If sedative drugs are taken in overdose, benzodiazepines may add to the risk of fatality
- Hypotension
- Respiratory depression
- Memory impairment
- Depression, emotional blunting
- Gastrointestinal, Genitourinary
- Tremor, dysarthria, visual disturbances
- Paradoxical stimulant effects → Possible increased risk of poor impulse control and hostility
- Tolerance
- Dependance

Risk Factors for Increased Adverse Effects

Conditions Associated	Risks
Older age (65 years and over)	Mental confusion, amnesia, ataxia, falls, and fractures.
Pregnancy	Neonatal CNS depression, withdrawal reactions in infant, floppy infant syndrome
Chronic respiratory disease	Respiratory depression.
Liver disease	Oversedation.
Depression	Aggravation of depression, precipitation of suicide.
History of alcohol or sedative abuse	Dependence & abuse
Alcohol or drug intoxication	Acute: CNS depression, excessive sedation
Personality disorder	Dependence, abuse, aggression.

Prof. C H Ashton, Psychiatric Annals Volume 25: pp158-165 March 1995

BPAC Advises Against BZD & Z-Drugs

- BPAC advises General Practitioners that they avoid starting benzodiazepines and zopiclone
- Once started they are hard to stop, especially of continued for long periods without review.
- If used, they should be prescribed at the lowest effective dose for the shortest possible time, ensuring the patient knows that they are not for long-term use.
- For older people already on these agents where withdrawal is not an option, slowly reducing the dose and providing advice and alternative strategies to enhance sleep can be effective in reducing falls.

BPJ 14, June 2009

Benzodiazepines and Z-Drugs

- Lader M. Benzos and Memory Loss: More Than Just 'Old Age.' Prescriber, 1992:3;13
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- Ashton H. The Diagnosis and Management of Benzodiazepine Dependence. Current Opinion in Psychiatry, 2005:18:249-255
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Z-Drugs

- The alpha-1 subtype of GABA receptor is highly expressed in the cortex and probably mediates the sedative and hypnotic effects of many drugs that act at the benzodiazepine site; zolpidem and zaleplon target this subtype preferentially (Sanna et al., 2002)
- Zopiclone does not show subtype selectivity but does exhibit a unique thermodynamic interaction with the benzodiazepine receptor that translates into less receptor adaptation on chronic dosing, and so less tolerance and withdrawal (Doble et al., 2003)
- The GABA(A) alpha-3 subtype predominates in the reticular nucleus of the thalamus, which plays an important role in regulating sleep. This subtype is particularly targeted by eszopiclone (Jia et al., 2009).

Z-Drugs

- Relative risk of Z-drugs misuse found to be one third that of benzodiazepine hypnotics. (Hajak, 2003)

- Z-drugs clearly emerge as being less liked and less sought after than the benzodiazepines by opiate users in treatment. (Jaffe, 2004)

Benzodiazepines, Z-Drugs & Sleep

- Decrease sleep latency
- Increase total sleep time
- Decrease wakefulness after sleep onset depending on half-life
- Subjectively, most users report high level of satisfaction.

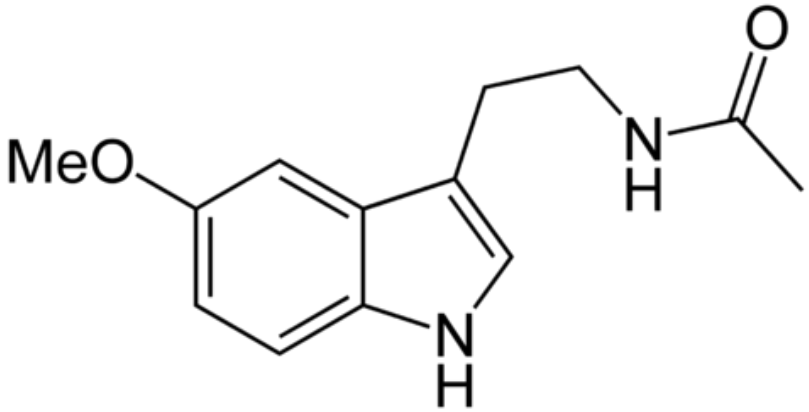
Guidelines for Hypnotics

- Use the lowest effective dose.
- Use intermittent dosing whenever possible,
  - Alternate nights or less.
- Prescribe short-term use in the majority of cases,
  - No more than four weeks.
- Discontinue slowly, especially from >4weeks use.
- Be alert for rebound insomnia or withdrawal.
- Advise on interaction with alcohol and other sedative agents.
- Avoid hypnotics in patients with respiratory disease or severe hepatic impairment, and in addiction-prone individuals.

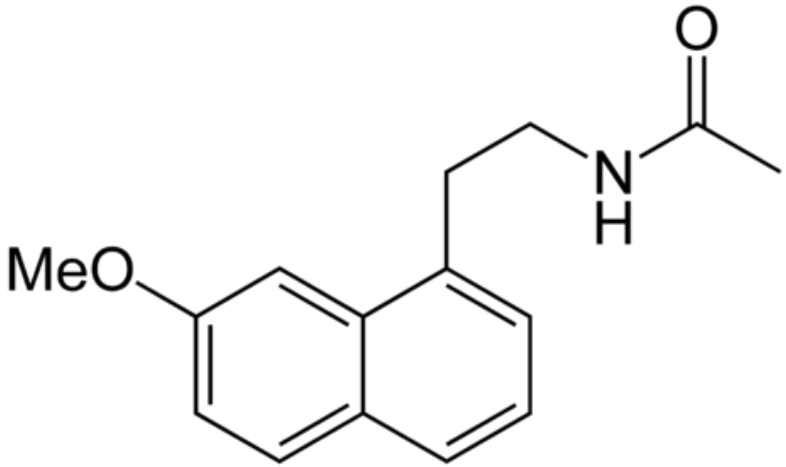
Melatonin

- Good evidence for use in sleep phase disorders.
- Not well evidenced in other insomnia, but;
  - Some people do well on melatonin,
  - May work well for older adults, or not,
  - We use for some patients on acute psychiatric unit.
- Less may be more with dose: 1mg nocte could be all that is required, 3mg preparation is available.
- Normal amount secreted is around 200-300micrograms.

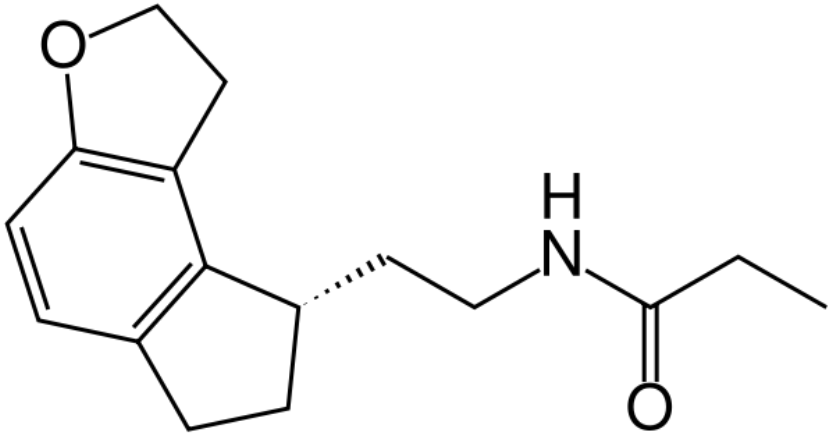
- Prescription medicine in New Zealand.
- Not subsidised in New Zealand, so shop around.
- Available as a Section 29 medicine.



Melatonin



Agomelatine: MT1 & MT2 agonist, 5HT2C antagonist



Ramelton: MT1 & MT2 agonist

Enhancing Sleep

- Address underlying medical and psychiatric conditions
- Learn mindfulness to calm mind; meditation, yoga, focus on the breathing (www.calm.auckland.ac.nz)
- Avoid stimulants; caffeine, nicotine, etc.
- Minimise alcohol intake.
- Bed firmness, temperature, noise.
- Minimise stimulating activities at night
- Go to bed when sleepy.
- Consistent sleep schedule.
- Keep the bed for sleep and sex ONLY.
- Avoid computer use into the night.
- Cell phones OFF!

Managing Insomnia

- What is causing the sleep symptom?
- Sleep hygiene
- Sleep CBT
- Judicious use of sedatives

Abbreviations

- CFS Chronic Fatigue Syndrome
- DSPD Delayed Sleep Phase Disorder
- EDS Excessive Daytime Sleepiness
- ME Myalgic Encephalopathy
- OSAS Obstructive Sleep Apnoea Syndrome
- PLMS Periodic Limb Movements in Sleep
- RLS Restless Legs Syndrome
- WASO Wakefulness After Sleep Onset

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Websites

- www.sleepfoundation.org (for patient information)
- www.insomniaspecialist.com
- www.nice.org.uk (for current best evidence guidelines)
- http://www.hauora.maori.nz/downloads/hauora_chapter13_web.pdf (prevalence in Maori)