Practical Approach to the Diagnosis and Management of Insomnia

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Chapter 114

What did Shakespeare, Van Gogh, Hemingway, Kafka, Napoleon and Marilyn Monroe have in common? They all had insomnia.1

INTRODUCTION
Insomnia is defined as persistent difficulty in falling asleep and staying asleep, with impairment of daytime functioning.1,2 A person suffering from insomnia wakes up frequently during the night or wakes up early and feels tired, sluggish and not refreshed, with an inability to concentrate. It is also one of the important causes of daytime sleepiness. The effects of insomnia can also include impaired mood and judgment and an increased likelihood of accidents at home and while driving or operating machinery.1,4 Studies have shown that people with insomnia suffer from more symptoms of anxiety and depression than people without insomnia. There can be a change in character and drop in quality of work, which may be misinterpreted as laziness or lack of motivation.1

Normal sleep requirement ranges between 6 hours and 8 hours, but many normal elderly people need only 4–5 hours. Ageing naturally tends to shorten the need for refreshing sleep. Older and elderly people can find that they sleep easier in the evening and wake much earlier the next morning, than in their 20s or 30s. This is physiological, but if the shortened period of sleep leaves the person tired and unrefreshed on waking up in the morning, the person suffers from insomnia. The highest level of insomnia happens in people aged 65 years and older.1 However, insomnia can occur at any age.

Chronic sleep disorder, especially insomnia, which affects some 70% of children with developmental or psychological disorders are underreported and undertreated.3 Insomnia can affect persons of all social strata.

Insomnia occurs in 30–45% adults, and its prevalence is about 1.5–2 times more common in females than males. Indian figures are unfortunately not known, but in the United States (US) alone, almost 60 millions people complain of insomnia.1

About 50% of the elderly population report insomnia.1 Though insomnia is a common symptom of depression, there is increased risk of subsequent depression, increased duration of established depression and relapse following treatment of depression in those depressed subjects who actually suffer from and complain of insomnia than in those who do not suffer from insomnia. Severe insomnia imposes a threefold to fivefold increased risk of hypertension.4

PATHOPHYSIOLOGY
Insomnia is associated with activation of hypothalamic-pituitary-adrenal axis with rise in levels of adrenocorticotropic hormone (ACTH) and cortisol.1

Insomnia results due to an imbalance between sleep inducing neurotransmitters [gamma-aminobutyric acid (GABA) and adenosine] present in the ventrolateral preoptic nucleus in the hypothalamus and the arousal neurotransmitters (noradrenaline, serotonin, acetylcholine, orexin and dopamine).4 Orexin also known as hypocretin, is a neuropeptide, which is liberated by a cluster of neurons in the lateral hypothalamus. It also appears to be involved in the control of wakefulness.

Sleep impairing effect of caffeine is thought to be due to blockade of adenosine A2 receptors.4

TYPES OF INSOMNIA
There are two types of insomnia: primary and secondary.3

Primary
When insomnia has no known physical (pain), emotional (depression/anxiety), environmental (noise at night) or chemical (drugs) cause, the condition is called primary insomnia.3

Secondary
Secondary insomnia is due to a known cause3,5 like:
- Emotional stress, anxiety, depression and other psychiatric disorders
- Dyspnea or orthopnea due to heart failure, chronic obstructive pulmonary disease (COPD) with cor pulmonale, bronchial asthma
- Alcoholism
- Painful conditions, e.g. arthropathy, postoperative pain, peptic ulcer
- Pregnancy
- Pruritus
- Neurodegenerative diseases (Parkinson’s disease, Alzheimer’s disease), stroke, headache syndrome, etc.

Insomnia can be transient (lasting < 2 weeks), short-term (lasting < 3 weeks) or chronic (lasting > 3 weeks).3

Transient insomnia or short-term insomnia is often linked to something that is happening to one’s life such as anxiety or stress about something like preparing for an examination, waiting for test results, starting a new medication or waiting for an operation. Once these situations are sorted out, the insomnia often passes. In some people, however, the short-term insomnia triggers anxiety about getting to sleep and this can contribute to chronic insomnia.

Even though, sleep medicine was recognized as a specialty by the 1970s in USA with founding of sleep laboratorie.; It is only lately being recognized as a field of expertise in the UK and India.6
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DIAGNOSTIC PARADIGM

Sleep Assessment Questions (Flow chart 1.)
Sleep assessment questions should include the following:
• Do you have difficulty falling asleep and staying asleep?
• Do you feel refreshed or not in the morning?
• Do you feel tired, during the day?
• Do you feel low and/or hopeless?
• Has anyone told you that you snore or stop breathing in your sleep?
• Do your legs often twitch and cannot keep still in bed while trying to sleep?
• Do you wake from sleep with jerky leg movements? [This will indicate restless leg syndrome and if the patient gets periodic limb movements in sleep it will indicate periodic leg movement disorder (PLMD)]
• Do you have pain in the joints or abdomen and back (to exclude painful arthropathy or peptic ulcer or lumbar spondylitis, etc.)?
• Do you get up many times during sleep due to acid regurgitation (gastroesophageal reflux disease)?
• Do you have nocturia, night sweats (and other menopausal symptoms)?

Personal History
Personal history of drinking alcohol late in the evening or consuming more than six caffeinated drinks in a day, going to bed hungry, smoking before bedtime, are all important as they induce insomnia.

History of Drug Therapy
Antidepressives like monoamine oxidase (MAO) inhibitors (phenelzine and tranylcypromine), selective serotonin reuptake inhibitors (SSRIs) like paroxetine (which sometimes causes restless leg syndrome), venlafaxine, second-generation antipsychotics like amisulpride and anxiolytics like buspirone, even in therapeutic doses cause insomnia in some individuals.

Environmental History
Inquiry should be made about disruptions in the sleeping environment at bedtime, e.g. noise around the bedroom, bright light, uncomfortable mattress, bed partner snoring, and also about shift work or jet lag, which may all cause insomnia.

Psychological History
The clinician should delve into the intimate aspect of the patients’ psychology—whether there has been bereavement in the family, any relationship problems, examination stress or work worries.

Clinical Examination
Thorough clinical examination to exclude evidence of heart failure, COPD, bronchial asthma, active arthropathy, peptic ulcer, Parkinson’s disease, dementia (including Alzheimer’s disease) is of prime importance as they constitute secondary causes of insomnia.

The physician should try to find positive evidence of depression like anhedonia, gloom, weepiness, suicidal ideations and of psychoses like hallucinations, delusions, withdrawal, ideas of reference, lack of insight, behavioral abnormalities including violent acts, etc.

Sleep Laboratory Tests

Polysomnogram
Polysomnogram (PSG) is an electrophysiological test that will differentiate primary insomnia from obstructive sleep apnea (OSA) and restless leg syndrome. Patient is admitted for the night, and whilst in bed, is attached with leads to the PSG machine. Patient is asked to go to sleep, while the instrument gets simultaneous records

Flow chart 1: Sleep assessment questionnaires with advice about referrals and about nonpharmacological treatment
of electroencephalogram (EEG), electrocardiogram (ECG), air flow and oxygen saturation, respiratory effort and leg movements, and electro-oculogram. The leads of PSG are attached to:
- Sites on scalp as for standard EEG
- Outer canthus of each eye
- Adjacent to nasal orifices
- Finger (pulse oximeter)
- Anterior chest wall near each shoulder and over apical area of heart
- Via nasal mask put over face connected to continuous-positive airway pressure (C-PAP) machine, which in turn is connected to the PSG machine for C-PAP titration.

Multiple Sleep Latency Test
This test measures the quantum of sleep deprivation or sleep debt. Some patients have unrealistic sleep expectations—they sleep well but still complain of insomnia and indulge in self-medication with over the counter formulations. This test identifies such patients and convinces them that they do not incur sleep debt. The subject is kept in a quiet, dark room and is asked to lie down in bed, close the eyes and relax. The number of minutes ranging from 0 to 20 that the subject takes to fall asleep is noted. If the subject is still awake after 20 minutes, the test is ended. Home testing of sleep latency can be done by a patient who reclines in a darkened room and drapes a hand, holding a spoon over the edge of the bed or chair, placing a plate on the floor vertically below the spoon. After checking the time, the subject tries to fall asleep. With the onset of sleep, the spoon will naturally strike the plate, awakening the subject, who then checks to see how much time has elapsed. The time passed is sleep onset latency (SOL). A SOL of 0–5 minutes indicates severe sleep deprivation, 5–10 minutes is troublesome, 10–15 minutes is indicative of little or no sleep-debt.8

Epworth Sleepiness Scale
Epworth sleepiness scale (ESS)10,11 test differentiates primary insomnia from OSA, narcolepsy and idiopathic hypersomnia (IH).

Epworth sleepiness scale is a scale intended to measure daytime sleepiness that is measured by use of a short questionnaire, which asks the subjects to rate their probability of falling asleep on a scale from 0 to 10 for eight different situations that most people engage during their lives, though not necessarily every day.

Numbers in the range 0–9 are considered to be normal, 11–15 indicate mild OSA, while a score above 16 indicates the possibility of severe OSA or narcolepsy (Table 1).

### MANAGEMENT
Nonpharmacological approach to insomnia care has been classified into two categories:
1. Sleep hygiene (SH)
2. Cognitive behavior therapy (CBT).

### Sleep Hygiene12
Patients should be educated about SH which comprises of the following:
- Taking a light exercise between 4 pm and 7 pm and never after 7 pm
- Going to bed when drowsy and at a proper time
- Removing the clock from the bedroom
- Switching off the (TV) and room light, etc.
- Avoiding more than six caffeinated drinks (coffee, tea, cola drinks) in a day and strictly avoiding these beverages and alcohol at bedtime
- Taking a light snack and/or milky drink before bedtime

### Pharmacotherapy
Hypnotics provide symptomatic relief and the following groups are usually recommended:
- Benzodiazepines7
- Z-hypnotics—nonbenzodiazepine compounds like zolpidem, zopiclone and zaleplon7
- Prolonged release melatonin7
- Antidepressants4
- Antipsychotics.4

**Benzodiazepines and Z-hypnotics**
They should be prescribed judiciously and at the lowest possible dose. They should not be continued, beyond 4 weeks.7

For transient insomnia, usually, the extraneous causative factors like noise and shift work should be taken care of. Jet lag usually subsides spontaneously in 2–3 days’ time. If a hypnotic is needed,
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one that is rapidly eliminated, should be chosen and only one or two doses should be given.8

After solving emotional problems and adding analgesics for painful physical conditions, a hypnotic can be tried. But hypnotics should not be continued for more than 3 weeks (preferably 1 week).9 Intermittent use is desirable with omission of some doses. A short-acting drug like zaleplon (5–10 mg), zolpidem tartrate (10 mg), lorazepam (1 mg) or temazepam (10 mg) at bedtime should be chosen. Zaleplon is the preferred option.8,9

Chronic insomnia is rarely benefitted by hypnotics,8 and is sometimes, due to mild dependence caused by injudicious prescription of hypnotics. Chronic insomnia due to anxiety should be treated with lorazepam (1 mg) at bedtime combined with chlordiazepoxide (10 mg) in the morning and/or at noon.

Chronic insomnia due to depression is characterized by early waking. Clomipramine or mirtazapine prescribed for depression will also help to promote sleep if taken at night. Organic comorbidities mentioned earlier as causes of insomnia should, of course, be taken care of.

Prolonged-release Melatonin
Melatonin is a hormone secreted by pineal gland. It is important in regulation of circadian rhythm and sleep function. It is a good drug for short-term uses up to 13 weeks for primary insomnia in patents aged 55 years or older.8 Prolonged release melatonin can be administered in dosage of 2 mgm once 1 to 2 hours before bed time8,9.

Cautions
• Side effect and cautions while prescribing the above should be remembered
• Hypnotics are not justified in children except for occasional use in insomnia due to night terrors and seizures8
• Z-hypnotics and benzodiazepines should be avoided in the elderly because they are at great risk of becoming ataxic and confused leading to falls and injuries (even fractures and head injuries).

All hypnotics are contraindicated in pregnancy as they may lead to neonatal hypothermia, hypotonia and respiratory depression. Neonatal withdrawal symptoms may occur if benzodiazepines are used during pregnancy. All hypnotics except zaleplon are excreted in breast milk, and therefore, breast-feeding or better still, the hypnotic should be avoided in lactation. Even melatonin is contraindicated during breast-feeding.8

Only short-acting hypnotics should be chosen for those who have to drive vehicles or operate dangerous machinery.

Recent studies have shown a possible association of an increased risk of cancer with Z-hypnotics.7

Melatonin should be avoided in diabetics, in persons with migraine, hypertension and arthritis and complete blood count should be monitored periodically as leukopenia and thrombocytopenia might complicate the therapy.5

Ramelteon (Licensed in USA) is an analog of melatonin.

Mode of Action of Above Drugs8
The sleep promoting effects of GABA are mediated through GABA receptors, which are of various types. Traditional benzodiazepines act on GABA types 1,2,3,5 receptors. Z-hypnotics act on GABA alpha 1 and 3 subtypes.

Melatonin8 and its analog ramelteon act as sleep promoters in the elderly because their melatonin production is reported to decline.

OTHER DRUGS USED FOR INSOMNIA

Antidepressants4
There is limited evidence for efficacy of doxepin, trimipramine and paroxetine (1b-level of evidence–based medicine). They are longer acting, longer than traditional hypnotic drugs. Trazodone is a better drug to promote sleep.4

Antipsychotics
Olanzapine and quetiapine improve sleep in primary insomnia (2b-level of evidence–based medicine), but have many side effects.

It is to be noted that concomitant CBT and pharmacotherapy will have additive effects.

Herbal remedies (e.g. valerian, chamomile, hop pillows) are not standardized, and are not necessarily safe, nor have fewer side effects than hypnotics, licensed for insomnia. Their efficacy is not proven.7

Minimizing Effects of Electromagnetic Pollution
Minimizing effects of electromagnetic pollution by moving all electrical appliances at least 6 feet away from the bed and by avoiding use of electric blankets may be helpful in insomnia.

Dark Therapy
Dark therapy13 is an experimental treatment, which involves eliminating all light in the subject’s environment for a period of 6–16 hours/day, in combination with a regular sleep schedule. It manipulates circadian rhythms action on hormones and

Yoga
Transcendental Meditation
Bhramri has advocated as treatment for chronic primary insomnia. Listening to cassettes of yoga-nidra at bedtime is also advocated. The author could not find any randomized controlled trials (RCTs) to validate these as effective treatment for insomnia.

Stress Reduction Techniques
Stress reduction techniques like breathing exercises (yogic pranayama), massage therapy or warm baths before bedtime may aid sleep.

Acupuncture
Acupuncture hypothetically increases level of central nervous system endorphins and this helps insomnia patients. No RCTs are available.

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neurotransmitters. It is hypothesized that the benefits of being in
the dark are due to melatonin production by the pineal gland, which
occurs when the eyes are deprived of light. Based on this hypothesis,
persons with insomnia due to disturbed sleep-awake circadian
rhythms, may benefit.

REFERENCES
sleepwelllivewell.co.uk/sleep-disorders/insomnia. [Accessed December, 2012].
2. Hirshkowitz M, Sharaikhaneh A. Neuropsychiatric aspects of sleep
Psychiatric Publishing Textbook of Neuropsychiatry and Behavioral
sleepwelllivewell.co.uk/sleep-disorders. [Accessed December, 2012].
Psychopharmacology consensus statement on evidence-based
treatment of insomnia, parasomnias and circadian rhythm disorders.
problems: symptoms, treatment, and help for common sleep disorders.
[Accessed December, 2012].
Available from www.guardian.co.uk/commentisfree/2008/jul/28/
7. Shneersonj Bromly J, Cannon P et al. Diagnosis and management of
insomnia in primary care, in the chapter Central Nervous System in the
(June), Natalie Hayeem (Ed) 47:2008 to 2013 published by MGP Ltd,
Salter, 263-265 High Street, Berkhamsted HP4 1AB available from www.
eguidelines.co.uk/about_guidelines/php [Accessed December 2012].
8. Woller DG. (2012). Central Nervous System: Anxiolytics; Drugs used in
psychoses and related disorders; and Antidepressant drugs. [online]
Available from www.asp.n.mobi/formulary/BNF%20Section%204.
Available from en.wikipedia.org/wiki/sleep_onset_latency. [Accessed
December, 2012].
10. Johns MW. A new method of measuring daytime sleepiness: the
Sleepiness Scale is and how to use it. [online] Available from
epworthsleepinessscale.com/about-epworth-sleepiness/. [Accessed
December, 2012].
[Accessed December, 2012].