Review Article

An Overview of Insomnia Management

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Sleep is one of the essential and basic physiological processes seen in higher animals. Since time immortal it is rightly believed that a full- night, refreshing sleep is necessary for adequate day time functioning. In the light of current understanding of neurobiology of sleep, it is not viewed as a mere passive state, rather an active neurobehavioral state that is maintained through highly organized interaction of neurons and neural circuits in the central nervous system.

Sleep disorders are both dangerous and expensive. Both short and long duration of sleep are associated with increased mortality, lowest risk being associated with 7 hours sleep[1,2]. Obstructive sleep apnoea has been shown to cause systemic hypertension[3], congestive heart failure[4] and stroke[5]. Troubled sleep was also associated with increased risk of work injury[6]. A strong temporal correlation between completed suicides and sleep problems[7]; insomnia and suicidal ideation in depressed population[8] have been demonstrated.

In this article we consider the management of insomnia, with special emphasis on pharmacotherapy.

Insomnia

Many definitions of insomnia are available. Few are mentioned below –

- Diagnostic and Statistical Manual – IV defines insomnia as difficulty initiating sleep or maintaining sleep or having non restorative sleep for 1 month or more[9].
- American Academy of Sleep Medicine defines insomnia as unsatisfactory sleep that impacts daytime functioning.

Insomnia is a common clinical problem and most common among sleep disorders. The National Institutes of Health (NIH) State of the Science Conference on the Manifestations and Management of Chronic Insomnia in Adults panel report states that insomnia is a problem occasionally, for approximately 30% of adults in the general population, that insomnia is a chronic problem for about 10% of adults, and that in clinical settings insomnia prevalence is roughly 50%[10]. Insomnia is relatively common in females, old age persons and persons of lower socio economic status[11]. It is also a common symptom among psychiatric patients with 50 to 80 percent of adult psychiatric population facing difficulty either in falling or staying asleep during any year[12]. Other risk factors include co-morbid medical conditions, being separated or divorced, chronic life stress and black race.[13,14]

Insomnia can be classified as co-morbid insomnia, which co occurs with medical and psychiatric conditions. Primary insomnia includes several insomnia diagnoses in the International Classification of Sleep Disorders including psychophysiologic insomnia, sleep-state misperception, idiopathic insomnia, and some cases of inadequate sleep hygiene. Idiopathic insomnia presents in childhood and has a lifelong course, presumably caused by an abnormality in the neurologic control of the sleep-wake system[15].

Insomnia can also be classified based on the duration. Transient insomnia is one which typically lasts for few days and is usually associated with brief adjustment reaction, rotating shifts or international travels. Short term insomnia is characterized by 4 to 28 days of poor sleep and most common precipitants being illness, bereavement, break in relationships etc[16]. Insomnia even longer lasting is classified as chronic insomnia.

One more way of classifying insomnia is depending on the time of the night the patient complains of sleep disturbances. Subtypes including difficulty in sleep onset, difficulty in maintenance and early morning awakening. This classification

helps in planning therapeutic interventions[15].

The DSM IV diagnostic criteria for primary insomnia are given in the Table 1.

and making a specific diagnosis of insomnia. On the basis of duration, insomnia is broadly divided in to two subtypes.

Table 1. – DSM IV Diagnostic criteria of primary insomnia[9]

- ❖ The predominant complaint is difficulty initiating or maintaining sleep or non-restorative sleep for at least 1 month.
- ❖ The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- ❖ The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia.
- ❖ The disturbance does not occur exclusively during the course of another mental disorder (eg, major depressive disorder, generalized anxiety disorder, or delirium).
- ❖ The disturbance is not caused by the direct physiologic effects of a substance (ie, drug abuse, medication) or a general medical condition.

Points to be considered in clinical evaluation of insomnia include[16]

- Detailed description of current symptoms including sleep problems, sleep habits, patterns and any emotional, physiological stresses surrounding sleep.
- Symptoms of other sleep disorders including snoring, witnessed breathing pauses, motor restlessness, involuntary leg movements etc.
- Day time consequences including mood disturbances, fatigue, cognitive difficulties.
- Careful evaluation of co morbid psychiatric and medical conditions.
- Any medications that can alter the normal sleep including caffeine, alcohol, and antidepressants like SSRIs and SNRIs.
- Collection of a 2-week sleep-wake diary, which is a prospective charting of a patient's actual sleep hours and habits, and it can usefully identify variability in sleep patterns and specific daytime correlates which may provide targets for subsequent intervention.
- Specific laboratory tests as needed including polysomnography.

Treatment approach of insomnia

The broad outline of insomnia management can be summarized as below[17].

History taking is very important in assessment

- ➢ Acute insomnia – Insomnia less than 30 days
- ➢ Chronic insomnia – Insomnia more than 30 days

Identification of stressors and appropriate intervention along with use of short acting hypnotics is helpful. But if with the above strategy becomes in effective then evaluation of sleep hygiene and possible co-morbid conditions is important. The Table 2 depicts important co-morbid conditions that need to be assessed.

Table 2. – Important co-morbid conditions[17]

Medical Disorders — Benign Hypertrophy of Prostrate, Congestive Heart Failure, Musculoskeletal disorders, Malignancies, Pain etc.
Psychiatric Co-Morbidities — Mood disorders, Substance abuse, Schizophrenia etc. Elderly population (specifically with Dementia)
Drug/Medication Use Other Conditions — Sleep apnoea, Restless leg syndrome, Periodic limb movement disorder etc.

The co-morbid conditions need to be treated adequately in order to manage insomnia. If with the above treatment strategy there is no improvement and the insomnia persists then it is require adopting the following treatment strategy as mentioned below in Table 3.

Non-pharmacological management of insomnia

Non pharmacological approaches are preferred

Table 3. - Treatment strategy

Sleep hygiene
Exercise
Non pharmacotherapy
Pharmacotherapy
Combination of above methods

by most insomnia patients[18]. Studies have also shown that non pharmacological methods are effective, both in primary and co-morbid insomnia and they are at least as effective as pharmacological treatments. The different non pharmacological methods are depicted below.

1. *Cognitive behaviour therapy* – focuses on correcting the incorrect beliefs, attitudes about sleep, techniques include reattribution training and decatastrophisation, reappraisal and attention shifting.
2. *Sleep restriction* – aimed at reducing the amount of time spent in bed. Bedtimes are then increased or decreased depending on the improvement or deterioration of sleep quality and duration
3. *Stimulus control therapy* – focuses on eliminating the environmental cues associated with arousal and aims to break the negative association of being unable to sleep[19] patient is instructed to avoid bright light, noise, extremes of temperature, large meals, caffeine, tobacco and alcohol at night.
4. *Relaxation therapy* – targets the cognitive or physiological arousal that interferes with sleep. A number of relaxation therapies have been used for insomnia, including PMR and biofeedback to diminish physiologic arousal, and imagery techniques, autogenic training, and meditation to reduce cognitive arousal. Relaxation techniques may be most useful for sleep onset insomnia[20]
5. *Temporal control measures* – Consistent time of wakening; minimal daytime napping
6. *Exercise* – Moderate-intensity exercise (should not occur just before bedtime)
7. *Chronotherapy* – Involves a progressive delay of bedtime, generally 3 hours per night, bringing patients all the way around the clock to the desired earlier bedtime[21].
8. *Light therapy* – Morning light exposure in individuals following a nocturnal sleep schedule tends to advance the circadian sleep phase. Evening light exposure, by contrast, tends to delay the circadian sleep phase[21].

Sleep hygiene education

It is the first choice once a full assessment has eliminated primary psychiatric or medical disorder. These are general guidelines; it is advised to focus one of two of these principles at a time. Long term outcome data is still scarce to support its use[22].sleep hygiene suggestions are depicted in the Table 4.

Table 4. – Suggestions for sleep hygiene

• Maintain regular hours of bedtime and arising
• Avoid heavy meals near bedtime; light snack can be taken if hungry.
• Avoid daytime napping
• Maintain regular exercise schedule
• Minimize caffeine intake and smoking near bedtime.
• Do not look at clock in night
• Make bedroom comfortable, preferably slightly cool
• Do not use alcohol while going to sleep
• Go to bed only when sleepy
• Minimize light, noise and excessive tempera-ture during sleep
• Avoid evening stimulation: substituted radio or relaxed reading for television. Practice evening relaxation routines. If you are worrying about something, write it down and deal with it next morning.

Pharmacotherapy of insomnia

Since centuries, many medications have been tried for relief of sleep. Yet the search for an ideal hypnotic is still on. Properties of an ideal hypnotic is listed in Table 5.

History of pharmacotherapy of insomnia

Over the centuries, various means of treating insomnia have been attempted, from ancient Aryuvedic Indian oils poured on the head to balance the humors, to comfrey and valerian used by folk healers in medieval times, to the ubiquitous nightcap[23].

Barbiturates were primarily used hypnotics till 1970s, when benzodiazepines took over. The latter

Table 5 – Properties of an ideal hypnotic

- Specific mechanism of action
- Rapid absorption
- Rapid sleep induction
- No residual effects
- Induces 'normal' sleep pattern
- Works through the night
- No ataxic effects
- No interaction with other drugs or alcohol
- No respiratory depression
- No rebound insomnia
- No dependence
- Safe in overdose

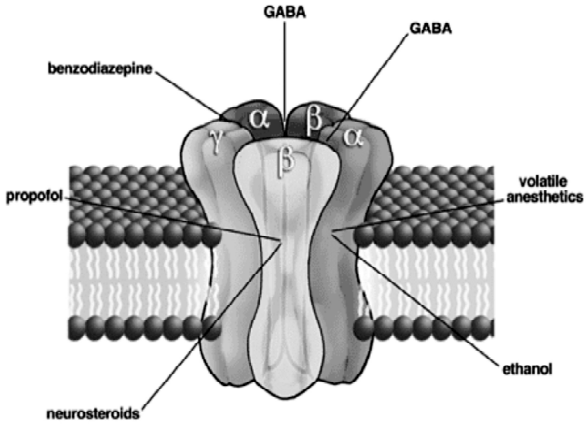

Fig-1. GABA receptor complex[50]

had advantages of less dependence, less tolerance risk, less respiratory depression. The rescheduling of hypnotic barbiturates to Schedule II under the Controlled Substances Act in 1973 also was a reason for drop in their use. Meanwhile, non barbiturate alternatives, such as glutethimide, chloral hydrate, and methaqualone, also saw a significant decline in number of prescriptions whereas, use of the antidepressants and anxiolytics increased[24].

A recent trend is that sedating antidepressants are more and more frequently used (an increase by 146% from 1987 to 1996) whereas use of FDA approved drugs of insomnia has dropped by 53%[25]. Also there was decline in the use of barbiturates, antihistamines and other drugs with sedating properties.

The pharmacological options available at present

Benzodiazepines

Five Benzodiazepines are approved for short term management of insomnia by FDA (mentioned in the Table 6). However, other benzodia-zepines, such as diazepam, lorazepam, and alprazolam also are also prescribed for insomnia symptoms.

They function as positive allosteric modulators of gamma-aminobutyric acid (GABA) responses at the $GABA_A$ receptor complex (Fig. 1), GABA being the most widespread CNS inhibitory neuro-transmitter. Several different types of GABA receptors have been identified, and these may exist in different configurations. The most common pentameric GABA receptor combination includes two alpha1, two β_2, and one γ_2 subunit. GABA on binding to postsynaptic GABA receptors causes an influx of chloride ions through the pore and into the postsynaptic neuron. This increased negative intracellular charge hyperpolarizes the cell, which inhibits neurotransmission.

The efficacy of Benzodiazepines is well established for relieving nocturnal symptoms of insomnia. Differences among Benzodiazepines are determined primarily by the pharmacokinetics of each drug, which influence rapidity of onset and duration of hypnotic action. Hypnotic efficacy of Benzodiazepines is supported by meta-analyses of PSG measures and patient reports[26].

All currently approved Benzodiazepines are absorbed rapidly, and thus, reduce sleep latency at recommended doses. The longer a drug's duration of action, the more sleep maintenance benefit is observed (ie, minimizing awakenings and WASO). Most Benzodiazepines increase total sleep time, the net result of affecting sleep onset and sleep maintenance. Zaleplon is an exception, which has a short duration of action and does not increase total sleep time reliably. This short duration of action, however, allows dosing for patients who may have only 4 to 5 hours left before they must rise in the

Table 6 – FDA approved benzodiazepines for insomnia

Drug	Dose Range	Elimination half life
Estazolam	1–2 mg	10 – 24 h
Flurazepam	15 – 30 mg	48 – 120 h #
Temazepam	15 – 30 mg	8 – 20 h
Triazolam	0.125 – 0.25 mg	2.4 h
Quazepam	7.5 – 15 mg	48 – 120 h #

Refers to elimination half-life of active metabolite desalkyl-flurazepam.

morning or in treating patients in whom morning sedation with longer-acting agents is a problem. If zaleplon is administered with at least 5 hours of potential time in bed remaining, the residual sleepiness at wake time is a minimal risk[27].

In the few longer studies conducted to date, Benzodiazepines seem to retain efficacy for at least several months[28,29]. Abuse of Benzodiazepines used for insomnia appears to be uncommon. One survey showed no greater use of increased doses for Benzodiazepines compared to antidepressants[30]. Although data are difficult to obtain, benzodiazepines may be used by 0.5% to 3% of the population for non-medical purposes in any one year[31]. Among individuals with no prior substance use history, abuse of Benzodiazepines appears to be uncommon.

Generally, the Benzodiazepines are well tolerated. Adverse effects may be in the form of somnolence, headache, dizziness, nausea, diarrhoea, and anterograde amnesia. Rarely patients may exhibit sleepwalking or confused behaviours within a few hours after taking a hypnotic dose. There are no equivocal reports to prove that benzodiazepines increase the risk of fall and fractures, and some studies suggest that insomnia itself is a risk factor for falling, hip fracture, and so forth. Brassington and colleagues[32] found that reported sleep problems, but not use of psychotropic medication, are independent risk factors for falls in community-dwelling adults over 64 years of age. One more recent study concluded that, the risk for falls is significantly higher for insomnia without hypnotic use and for insomnia with hypnotic use, but not for hypnotics who did not have insomnia[33].

Rebound insomnia refers to a worsening beyond pre-treatment measures when a drug is discontinued abruptly, frequently seen after withdrawal of a short-acting or intermediate-acting drug, and the likelihood and severity of rebound is related to hypnotic dose but not necessarily the duration of use. Gradual tapering down of the dose prevents rebound. Plasma concentrations slowly decline in the longer acting drugs and rebound is unlikely[26].

The "Z series" drugs

These nonbenzodiazepines selectively bind to type 1 benzodiazepine receptors in the CNS and unlike benzodiazepines they have minimal impact on sleep stages and do not cause REM sleep rebound. Non-benzodiazepines are similarly effective but have less overall risk of adverse effects[36]. Nevertheless, these newer agents can cause impaired memory and psychomotor retardation[37]. Zolpidem, Zaleplon, and Eszopiclone have been approved by FDA for insomnia.

Zolpidem – It decreases sleep-onset latency, improves sleep quality, increases stage 2 and slow-wave sleep. No tolerance or rebound insomnia exhibited following five weeks of continuous use at recommended dosages[35,36]. Adverse effects occur at daily dosages of 20 mg or more. A controlled-release version in a dosage of 6.25 to 12.5 mg daily may be better for maintaining sleep, but it should not be re-administered following nocturnal awakenings and has not been shown to reduce adverse effects[38]

Zaleplon- It decreases sleep-onset latency. Its short half-life (i.e., one hour) enables re-administration following nocturnal awakenings. It is particularly useful in patients who have trouble falling asleep and maintaining sleep and can be administered up to four hours before the anticipated wake time[38]. It produces less memory and psychomotor impairment than has been observed with benzodiazepines and Zolpidem[39].

Eszopiclone – An isomer of zopiclone, is the only hypnotic with FDA approval for use longer than 35 days. Eszopiclone has evidence of effectiveness for six months of therapy in a randomized, placebo-controlled trial, although there is some attenuation of its effect over time. It produces significant and sustained decreases in sleep-onset latency, wake time, number of awakenings, and number of nights awakened per week; it also improves total sleep time and quality of sleep[40].

Higher doses (2 to 3 mg) are more effective for sleep maintenance, whereas lower doses (1 to 2 mg) are suitable for difficulty in falling asleep. The onset of action may be delayed if eszopiclone is taken with a high-fat meal. Rare cases of fatal overdose when used with other CNS depressants have been reported.

Sedating Antidepressants

Sedating antidepressants commonly are used off-label to treat insomnia. Several factors likely

contribute to their use by physicians in spite of the absence of an established efficacious dose. The absence of cautionary language, misperception that sedating antidepressants are safer than Benzodiazepines and carry a lower risk for dependence and insomnia frequently interpreted solely as a manifestation of depression[25].

Among the sedating antidepressants prescribed for the treatment of insomnia, Trazodone, Amitriptyline, and Mirtazapine are used most commonly[34]. Trazodone is generally prescribed at doses far below the range typically needed for the treatment of depression and often in the absence of other antidepressant medications, suggesting its use to treat insomnia in patients who are not depressed.

These drugs produce sedation by blocking acetylcholine, norepinephrine, and serotonin presynaptic receptors. Compared with placebo, antidepressants decrease sleep-onset latency and wakefulness after sleep onset. They also increase total sleep time, sleep efficiency, and sleep quality but suppress REM sleep[35] and are effective and useful to treat insomnia in depressed patients.

The antidepressants as a class have more frequent and troublesome side effects in comparison to Benzodiazepines[26]. In trials of tricyclics used to treat primary insomnia, however, there are reports of leucopenia, thrombocytopenia, increased liver enzymes with doxepin[36]; dizziness, dry mouth, and nausea with trimipramine [36]; and daytime somnolence and weight gain with mirtazapine [36]. Data is also lacking to support the safety of trazadone, the adverse effects being orthostatic hypotension, cardiac conduction abnormalities, and priapism[37], hence use of antidepressants for treatment of primary insomnia is debatable.

Other drugs used for insomnia

Antihistamines, atypical antipsychotics, muscle relaxants, alcohol, herbal supplements are being used for insomnia, though there are no evidences regarding their efficacy and safety as hypnotics.

Regarding Diphenhydramine, though few poorly designed studies have shown improvement in general condition and subjective sleep latency and sleep quality[42,41], tolerance to hypnotic action is clearly evident to develop as early as 3rd day.[43,44] Antihistamines act by nullifying the wakefulness maintenance action of histamine.

Antipsychotics like Olanzapine and Quetiapine, though found to improve subjective measures of sleep in two small open labelled studies, their broad side effect profile, risk of metabolic syndrome and residual sedation due to long half life are the matters of concern.[45.46] Hypnotic action of atypical antipsychotics is also due to their antihistaminic property.

Alcohol is also commonly used as hypnotic. The significant problems with alcohol being tolerance, exacerbation of other sleep disorders (restless leg syndrome and obstructive sleep apnoea).

Future options

Ramelteon, a Melatonin Receptor Agonist, was FDA approved in July of 2005, for the treatment of insomnia characterized by difficulty with sleep onset. It selectively acts on MT1 and MT2 receptors, implemented in sleep and circadian rhythm.[47] Studies in primary insomniacs indicate that doses of 4 to 32 mg produce a modest yet significant reduction in PSG sleep latency[48] that is maintained for up to 5 week. There has been no differences in the sleep latency over the dosage range of 4 to 32 mg. Ramelteon seems to, produce phase advance at doses as low as 4 mg[48] , potentially explaining ramelteon's ability to promote sleep without appreciable sedation.

No potential for abuse relative to placebo and no withdrawal symptoms or rebound insomnia have been reported.[49] It is found to increase prolactin levels in adult women and reduce testosterone levels in adult men. But the clinical significance of these findings is not known. Ramelteon undergoes hepatic metabolism at cytochrome P450 1A2 (CYP1A2). Caution is recommended for patients who have at least moderate liver disease. Fluvoxamine inhibits CYP1A2, dramatically increasing the serum concentration of ramelteon, and co-administration with potent CYP1A2 inhibitors should be avoided.

Conclusion

Insomnia is a common problem that a clinician comes across. It has got physical psychological and financial implications for the sufferer and hence detailed evaluation and management are essential. Though a variety of pharmacological and non pharmacological treatment measures are available

yet treatment of chronic insomnia is a challenge. A skilful combination of both the measures is more beneficial to patient.

References

1. Hammond EC. Some Preliminary Findings on Physical Complaints from a Prospective Study of 1,064,004 Men and Women. Am J Public Health Nations Health 1964; 54 : 11–23.
2. Kripke DF, Simons RN, Garfinkel L, Hammond EC. Short and long sleep and sleeping pills. Is increased mortality associated? Arch Gen Psychiatry 1979; 36(1) : 103–116.
3. Lavie P, Here P, Hoffstein V. Obstructive Sleep Apnea Syndrome as a Risk Factor for Hypertension. Br Med. J 2000; 320 : 479–482.
4. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered Breathing and Cardiovascular Disease. Cross-sectional Results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001; 163 : 19–25.
5. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005; 353(19) : 2034–2041.
6. Kling RN; McLeod CB. Koehoorn M. Sleep problems and workplace injuries in Canada. Sleep 2010; 33(5) : 611-618.
7. Tina R. Goldstein, Jeffrey A. Bridge, David A. Brent; Sleep Disturbance Preceding Completed Suicide in Adolescents. J Consult Clin Psychol. 2008 February; 76(1) : 84. doi:10.1037/0022-006X.76.1.84.
8. Vaughn W, McCall et al. Insomnia Severity is an Indicator of Suicidal Ideation During a Depression Clinical Trial. Sleep Med 2010 October; 11(9) : 822–827. doi:10.1016/j.
9. American Psychiatric Association. Diagnostic and Statistical Manual IV Text Revision (DSM IV TR) Washington DC: American Psychiatric Association 2000.
10. National Institutes of Health State of the Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults, J Sleep 2005; 28 : 1049-57.
11. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 2002; 6 : 97–111.
12. Smith MT, Perlis ML, Park A, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. Am J Psychiatry 2002; 150 : 5–11.
13. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 2002; 6 : 97–111.
14. Buysse DJ, Germain A, Moul DE. Diagnosis, epidemiology, and consequences of insomnia. Prim Psychiatry 2005; 12 : 37–44.
15. Becker PM. Insomnia: Prevalence, Impact, Pathogenesis, Differential Diagnosis, and Evaluation; Psychiatr Clin N Am 2006; 855–870.
16. Buysse DJ, Chronic Insomnia. Am J Psychiatry 2008; 165(6) : 678–686. doi:10.1176/appi.ajp.2008.08010129.
17. Kalyanakrishnan Ramakrishnan, Dewey C. Scheid. Treatment Options for Insomnia; Am Fam Physician 2007; 76 : 517-26, 527-8.
18. Morin CM, Gaulier B. Barry T et al. Patient's acceptance of psychological and pharmacological therapies for insomnia. Sleep 1992; 302-305.
19. Bootzin RR, Perlis ML. Nonpharmacologic treatments of insomnia. J Clin Psychiatry 1992; 53 (suppl): 37-41.
20. Morin CM, Culbert JP, Schwarts SM. Non-pharmacological intervention for insomnia: a metaanalysis of treatment efficacy. Am J Psychiatry 1994; 151 : 1172-1180.
21. Nofzinger EA, Buysse DJ, Germain A, et al. Increased activation of anterior paralimbic and executive cortex from waking to rapid eye movement sleep in depression. Arch Gen Psychiatry 2004; 61 : 695–702.
22. Sharma S, Trivedi JK. Guidelines for the treatment of sleep disorders; www.indianj psychiatry.org/cpg/cpg2006/cpg-mgmt_16.pdf
23. Denise Troy Curry, Rhody D. Eisenstein, James K. Walsh. Pharmacologic Management of Insomnia: Past, Present, and Future. Psychiatr Clin N Am 2006; 29 : 871–893.
24. Institute of Medicine. Sleeping pills, insomnia, and medical practice.Washington, DC: National Academy of Sciences; 1979.
25. Walsh JK, Schweitzer PK. Ten year trends in the pharmacologic treatment of insomnia. Sleep 1999; 22 : 371–5.
26. Nowell PD, Mazumdar S, Buysse DJ, et al.

Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy [review]. JAMA 1997; 278 : 2170–7.
27. Walsh JK, Pollack CP, Scharf MB, et al. Lack of residual sedation following middle of the night zaleplon administration in sleep maintenance insomnia. Clin Neuropharmacol 2000; 23 : 17–21.
28. Oswald I, French C, Adam K, et al. Benzodiazepine hypnotics remain effective for 24 weeks. Br Med J (Clin Res Ed) 1982; 284 : 860–3.
29. Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over six months of nightly treatment: results of a randomized, placebo-controlled study in adults with chronic insomnia. Sleep 2003; 26 : 793–9.
30. Baiter MB, Uhlenhuth EH. Prescribing and use of benzodiazepines: an epidemiologic perspective. J Psychoactive Drugs 1992; 24 : 63-64.
31. Woods JH, Winger G. Current benzodiazepines issues. Psychopharmacology 1995; 118 : 107-115, 118.
32. Brassington GS, King AC, Bliwise DL. Sleep problems as a risk factor for falls in a sample of community-dwelling adults aged 64–99 years. J Am Geriatr Soc 2000; 48 : 1234–40.
33. Avidan AY, Fries BE, James ML, et al. Insomnia and hypnotic use, recorded in the minimum data set, as predictors of falls and hip fractures in Michigan nursing homes. J Am Geriatr Soc 2005; 53 : 955–62.
34. Walsh JK, Schweitzer PK. Ten year trends in the pharmacologic treatment of insomnia. Sleep 1999; 22 : 371–5.
35. Buscemi N, Vandermeer B, Friesen C, et al. Manifestations and management of chronic insomnia in adults. Evid Rep Technol Assess (Summ) 2005; 125 : 1-10.
36. Scharf MB, Roth T, Vogel GW, Walsh JK. A multicenter, placebo-controlled study evaluating zolpidem in the treatment of chronic insomnia. J Clin Psychiatry 1994; 55 : 192-9.
37. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. Clin Pharmacokinet 2004; 43 : 227-38.
38. Morin AK. Strategies for treating chronic insomnia. Am J Manag Care 2006; 12(8 suppl) : S230-45.
39. Toner LC, Tsambiras BM, Catalano G. Central nervous system side effects associated with zolpidem treatment. Clin Neuropharmacol 2000; 23 : 54-8.
40. Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. Sleep 2003; 26 : 793-9.
41. Kudo Y, Kurihara M. Clinical evaluation of diphenhydramine hydrochloride for the treatment of insomnia in psychiatric patients: a double-blind study. J Clin Pharmacol 1990; 30 : 1041–8.
42. Rickels K, Morris RJ, Newman H, et al. Diphenhydramine in insomniac family practice patients: a double-blind study. J Clin Pharmacol 1983; 23 : 234 - 42.
43. Schweitzer PK, Muehlbach MJ, Walsh JK. Sleepiness and performance during three-day administration of cetirizine or diphenhydramine. J Allergy Clin Immunol 1994; 94 : 716–24.
44. Richardson GS, Roehrs TA, Rosenthal L, et al. Tolerance to daytime sedative effects of H1 antihistamines. J Clin Psychopharmacol 2002; 22 : 511–5.
45. Juri C, Chana P, Tapia J, et al. Quetiapine for Insomnia in Parkinson Disease: results from an open-label trial. Clin Neuropharmacol 2005; 28 : 185–7.
46. Estivill E, de la Fuente V, Segarra F, et al. The use of olanzapine in sleep disorders. An open trial with nine patients. Rev Neurol 2004; 38 : 829–31.
47. Kato K, Hirai K, Nishiyama K, et al. Neurochemical properties of ramelteon (TAK-375), a selective MT1/MT2 receptor agonist. Neuropharmacology 2005; 48 : 301–10.
48. Erman M, Seiden D, Zammit G. Phase II study of the selective ML-1 receptor agonist TAK-375 in subjects with primary chronic insomnia [abstract]. Sleep 2003; 26(Suppl) : A298.
49. Gary Zammit, Milton Erman, Sherry Wang-Weigand et al. Evaluation of the Efficacy and Safety of Ramelteon in Subjects with Chronic Insomnia. JCSM 2007; 3(6) : 595-602.