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REVIEW ARTICLE

ZOLPIDEM IS AN EFFECTIVE OPTION WITH A REDUCED RISK FOR DEPENDENCE IN THE TREATMENT OF INSOMNIA***Alam Md Shadab¹, Sinha Ritesh kumar², Chandra Satish³, Hedayetullah Syed⁴, Khan Md Rashid Haider⁵**¹Junior Resident, Department of Pharmacology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India²Junior Resident, Department of Pharmacology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India³Professor, Department of Pharmacology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India⁴Medical officer incharge, Community Health Centre, Mandu, Ramgarh, Jharkhand, India⁵Pharmacovigilance Technical Associate, ADR Monitoring Centre, RIMS, Ranchi, Jharkhand, India**Corresponding Author's Email: shadab2k2rims@gmail.com***ABSTRACT:**

Insomnia is a highly prevalent sleep disorder that frequently occurs in its acute form and occurs at a rate of approximately 10 per cent in its chronic form in many countries. There is a high prevalence of insomnia in a variety of medical and psychiatric conditions for which insomnia often serves as a risk factor. There are various types of insomnia which are categorized in terms of how it affects sleep it has been shown to negatively affect many physiological, cognitive, and behavioural measures within the body. Recent years have observed that there is sudden increase of various diseases like hypertension, Heart attack, Obesity, Diabetes etc which occurs as a result of insomnia. Hence its impact on financial, social and psychological status of patients and their caregivers cannot be ignored. Thus finding a novel way to tackle these health problems is the need of present times. The most commonly prescribed medications for insomnia are the benzodiazepines (BZP) such as temazepam and diazepam. Although these medications are efficacious, they are associated with tolerance, dependence, residual daytime sedative effects, cognitive and psychomotor impairment, and discontinuation syndromes including rebound insomnia and withdrawal symptoms. For this reason, BZD use should be judicious and is replaced by Zolpidem, a novel non-benzodiazepine hypnotics of Imidazopyridine class that has various advantages over benzodiazepines. Chronic administration of zolpidem produces neither tolerance to its sedative effects nor signs of withdrawal when the drug is discontinued. Also it has little effect on the stages of sleep in normal human subjects. The drug is as effective as benzodiazepines in shortening sleep latency and prolonging total sleep time in patients with insomnia. Tolerance and physical dependence develop only rarely and under unusual circumstances.

Keywords: Insomnia, sleep disorder, benzodiazepines, tolerance, dependence, zolpidem, Imidazopyridine**INTRODUCTION:**

Humans sleep approximately one-third of their lives. Natural sleep patterns show considerable individual variability. Most adults are comfortable with 6.5-8 hours of sleep daily, taken in a single period.¹ Scientists do not fully understand the necessity for sleep, nor the mechanisms for sleep's physical and mental restoration. Sleep deprivation creates fatigue and suboptimal performance, causing significant medical, psychological, and social disturbances.^{2,3}

Insomnia is the second most common medical complaint with almost one half of the older adults experiencing symptoms of insomnia on a few nights a week. Insomnia is an inability to get the amount of sleep needed to function efficiently during the daytime. People with insomnia will often experience difficulty falling asleep, frequent awakenings during the night, early morning awakenings, insufficient sleep, day time exhaustion, lack

of concentration, nervousness, depression and forgetfulness. It affects millions of people about one-third of the adults in the United States. Many older people suffer from insomnia since it tends to increase with age and occur more frequently in people over age 60.

Insomnia is rarely a "primary disease"-meaning an isolated medical or mental illness-but rather a symptom of another illness to be investigated by a person and their medical doctors. In other people, insomnia can be a result of a person's lifestyle or work schedule.

There are different types of insomnia. Insomnia can be caused by many different conditions other than age, for example, an underlying physical or medical problem, stress, depression or other mental disorder, environmental noise, extreme temperatures, a change in the surrounding environment, medication side effects,

shift work or other night-time activity schedules, or jet lag.

Management of acute insomnia has traditionally involved pharmacotherapy. The use of such agents is common practice for both acute and chronic insomnia. Despite the fact that the benzodiazepines (BZP) such as temazepam and diazepam are used in the treatment of insomnia but on chronic use they are associated with tolerance, dependence, residual daytime sedative effects, cognitive and psychomotor impairment, and discontinuation syndromes including rebound insomnia and withdrawal symptoms. For this reason, BZD use should be judicious and is replaced by Zolpidem, a novel non-benzodiazepine hypnotics of Imidazopyridine class that has various advantages over benzodiazepines. Chronic administration of zolpidem produces neither tolerance to its sedative effects nor signs of withdrawal when the drug is discontinued. Also it has little effect on the stages of sleep in normal human subjects. The drug is as effective as benzodiazepines in shortening sleep latency and prolonging total sleep time in patients with insomnia. Tolerance and physical dependence develop only rarely and under unusual circumstances. So Zolpidem is an effective option with a reduced risk for dependence in the treatment of insomnia.

Definition of insomnia: Diagnostic criteria:-⁴

DSM-IV defines insomnia as difficulty initiating sleep or maintaining sleep or having non-restorative sleep for 1 month or more. The insomnia or resulting sleepiness must cause clinically significant impairment or distress in social, occupational, or other important areas of functioning.

International Classification of Diseases ICD-10 (1992) defines insomnia as Difficulty falling asleep, maintaining sleep or Non-refreshing sleep for 3 times a week and for longer than 1 month. There is marked personal distress or interference with personal functioning in daily living.

International Classification of Sleep Disorders (ICSD) and Research Diagnostic Criteria for Insomnia (RDC)⁵ defines insomnia as Difficulty initiating sleep, maintaining sleep, waking up too early or sleep is chronically non-restorative or poor in quality and Occurs despite adequate opportunity and circumstances for sleep. And, there is

At least one form of daytime impairment

- i. Fatigue or malaise
- ii. Attention, concentration, or memory impairment
- iii. Social or vocational dysfunction or poor school performance
- iv. Mood disturbance or irritability
- v. Daytime sleepiness
- vi. Motivation, energy, or initiative reduction
- vii. Proneness for errors or accidents at work or while driving
- viii. Tension, headaches, or gastrointestinal symptoms in response to sleep loss

ix. Concerns or worries about sleep.

Epidemiology of insomnia:-

Insomnia is the most common sleep disorder and one of those with the greatest health and social significance. The patient with insomnia complains primarily of dissatisfaction with the quality and or quantity of sleep. This dissatisfaction may stem from the difficulty in falling or staying asleep throughout the night, or the number of times patients wake up during the night.

To understand the epidemiology of insomnia it helps to understand the clinical relevance of this disorder.

Prevalence of Insomnia:-

Insomnia, or inability to sleep, is the most commonly reported sleep problem in the industrialized world.⁶ Estimates suggest that between 40 and 70 million Americans are affected by either intermittent or chronic sleep problems, representing approximately 20 percent of the population.⁷ The Sleep in America Poll, conducted by the National Sleep Foundation, revealed that almost 50 percent of people surveyed had complaints of frequent insomnia, but only 6 percent were formally diagnosed.⁸ Moreover, approximately, 30 to 35 percent of respondents complained of nightly insomnia. The most prevalent symptoms of insomnia, experienced at least a few nights a week by people with insomnia, include waking up feeling unrefreshed (34%) and being awake often during the night (32%). The symptoms of difficulty falling asleep and waking up too early are less common, but still experienced at least a few nights a week by about one-fourth of adults with insomnia (23 to 24%).

There is emerging evidence that short-term sleep deprivation, under strict experimental conditions, is associated with a variety of adverse physiological and cognitive effects. Decrements in memory, concentration and executive function have been reported. There is also an increased risk of injury and accidents. Physiological effects resulting from sleep deprivation include hypertension, activation of the sympathetic nervous system, altered glucose metabolism and increased inflammatory markers. Sleep deprivation is associated with excessive sleepiness. Acute insomnia, however, may not equate to sleep deprivation. There is no evidence to suggest that patients with insomnia experience similar changes. Furthermore, it is not yet clear from the evidence what the physiological consequences of chronic insomnia are or if there is a process of adaptation that occurs in individuals with chronic insomnia. Thus, further research is needed in the area of chronic insomnia to determine what impact chronic insomnia has on health.

Risk Factors for Insomnia:-

Although some risk factors and etiologies of insomnia have been identified, the nature of the relationships has not been fully elucidated. Some risk factors for insomnia that have emerged from data related to insomnia include female gender and old age.⁹ Additional risks factors include:-

- **Medical disorders:** CHF, COPD, asthma, GERD, cancer, chronic pain, hyperthyroidism, BPH, Parkinson's disease, fibromyalgia.
- **Primary sleep disorder:** OSA, RLS, periodic limb movement disorder.
- **Psychiatric disorders**
- **Sleep wake disorders:** Irregular sleep-wake cycle, jet lag, shift work.
- **Substance Abuse**
- **Medications:** Anticholinergics, antidepressants, antiepileptic, CNS stimulants, steroids, bronchodilators, diuretics, etc.

Classification of Insomnia:-

There are many ways to classify insomnia, but for practical purposes they can be classified according to etiology, time of night when it occurs or duration.

According to etiology:-

- **Primary insomnia:-** Which doesn't have a clearly identifiable etiological factor or is not associated with any other medical condition.
- **Secondary insomnia:-** SI is the term given to cases of insomnia that appear to be secondary to other distressful conditions or secondary to substance use. 'Secondary' in this context means that another condition causes and maintains the insomnia. Insomnia cases where no causal link exists, but where insomnia and another condition co-occur yet function independently, are referred to as 'comorbid'. If an insomnia state is clearly secondary to another condition, then presumably, the insomnia will subside if the primary condition is successfully treated, but data to support this SI conceptual scheme are scarce, calling into question the concept of causal influence in supposed SI.

According to duration:-

- **Transient insomnia:-** Lasting less than a week. This is the most common and widespread form among the population. In a period of one year, about one-third of adult population have a problem with insomnia, and, of those, about half have what is known as transient insomnia. It is often associated with precipitating stressors (e.g. environmental causes, sudden changes in sleeping time, occasional physical stress, and emotional crisis) and when they disappear sleep returns to normal.
- **Short term or acute insomnia:-** Lasting between one and four weeks. It is related to stress factors, but longer lasting than for transitory insomnia.
- **Chronic insomnia:-** Lasts for four or more weeks and may be due to intrinsic cause in the organism e.g. a long term physical or psychiatric illness or it may have no apparent underlying cause.

According to time of night when it occurs:-

- **Falling asleep:-** The patient's complaints refer to difficulties in starting sleep. This is the most common form of insomnia associated with medical problems, drug abuse, or certain psychiatric disorder such as anxiety disorder. Such types of insomnia usually occur in the young.

- **Staying asleep:-** the patient has difficulty in maintain sleep with frequent interruption or wakefulness during the night. It is common in cases of psychological or medical problems associated with ageing.
- **Waking up early:-** when waking occurs at least two hours earlier than normal.

Other Classification of Insomnia:-

- Adjustment Insomnia
- Psycho physiological Insomnia
- Paradoxical Insomnia
- Idiopathic Insomnia
- Insomnia Due to Mental Disorder
- Inadequate Sleep Hygiene
- Behavioural Insomnia of Childhood
- Insomnia Due to Drug or Substance
- Insomnia Due to Medical Condition
- Insomnia Not Due to Substance or Known Physiological Condition, Unspecified (*Nonorganic Insomnia, NOS*)
- Physiological (*Organic*) Insomnia, Unspecified.

Symptoms of insomnia:-

- Difficulty falling asleep
- Frequent awakenings during the night
- Early morning awakenings
- Insufficient sleep
- Daytime exhaustion
- Lack of concentration
- Grouchiness or nervousness
- Depression
- Forgetfulness
- Fatigue
- Excessive Daytime Sleepiness
- Major and/or Minor Depressive Episode
- Generalized Anxiety Disorder
- Memory/Concentration
- Pain

The assessment of insomnia:-

An insomnia assessment includes a thorough sleep, medical and psychiatric history.¹⁰ The sleep history can begin with a chronological review of sleep starting with childhood and may also include: identifying any factors that precipitated the insomnia (and whether these factors are still present), current life stressors, factors currently thought to be contributing to insomnia, a description of a typical 24-hr period in terms of sleep behaviours and schedule, how often a typical night occurs, how a bad night differs from a good night, if there are any identifiable weekly, monthly or seasonal sleep patterns, what has been tried to correct the sleep disturbance and to what extent such strategies worked. A sleep history also includes questions to rule out other possible sleep disorders. Differential diagnosis also includes distinguishing the primary insomnias from a co-morbid insomnia. Some of these conditions do warrant targeted intervention prior to treating the presenting insomnia. Typical exclusions for initiating insomnia treatment include untreated or unstable medical, psychiatric or substance abuse conditions (e.g., gastroesophageal reflux disease, cardiopulmonary disorders, seizure disorders, some neuroendocrine disorders, sleep apnoea, bipolar

disorder, severe mental illness, active substance dependence). It is imperative to note that co-morbid insomnia may nonetheless be treated in conjunction with the treatment of a 'primary' disorder or even as a front line intervention. Numerous self-report instruments exist for the assessment of sleep disturbance. Among the most widely used are the Pittsburgh Sleep Quality Index,¹¹ which provides a global assessment of sleep, and the Insomnia Severity Index,¹² specifically designed for insomnia. Perhaps the most useful self-report measure is a daily sleep diary, which patients are asked to complete on a daily basis for 1-2 wk. At a minimum, a sleep diary assesses time to bed, minutes to fall asleep, number and duration of awakenings, final awakening and time out of bed. From these data, averaged over the 1-2 wk period, a patient's sleep continuity can be determined. This includes latency to sleep, wake time, average time in

bed, total sleep time, sleep efficiency (sleep time divided by time in bed). Objective measures of sleep can be obtained via wrist-worn actigraphy. Although not as informative as a full night polysomnographic recording, actigraphy can corroborate or replace sleep diary data. Unless paradoxical insomnia or another sleep disorder (e.g., sleep apnoea) is suspected, polysomnography is not indicated in the assessment of insomnia. An important consideration for the general, family, or other primary care practitioner is that any evaluation of sleep is not the norm in standard practice. Therefore, even asking a simple question such as "how are you

Sleeping?" can begin to unmask chronic insomnia. Given the prevalence of insomnia, this can be a valuable conversation starter that leads to a more thorough sleep assessment or a referral based on the providers preference for managing insomnia in their practice.

Insomnia severity index:-

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you have your total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?
 Very Satisfied Satisfied Moderately Satisfied Dissatisfied Very Dissatisfied
 0 1 2 3 4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?
 Not at all Noticeable A Little Somewhat Much Very Much Noticeable
 0 1 2 3 4

6. How WORRIED/DISTRESSED are you about your current sleep problem?
 Not at all Worried A Little Somewhat Much Very Much Worried
 0 1 2 3 4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?
 Not at all Interfering A Little Somewhat Much Very Much Interfering
 0 1 2 3 4

Guidelines for Scoring/Interpretation:

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 + 6 + 7) = _____ your total score

- Total score categories:
 0–7 = No clinically significant insomnia
 8–14 = Subthreshold insomnia
 15–21 = Clinical insomnia (moderate severity)
 22–28 = Clinical insomnia (severe)

Pathophysiology of insomnia:-

There is currently no single, cognitive-behavioural model of insomnia. Instead, a number of related and overlapping models are available. All such models consider insomnia a condition that develops over time, is related to maladaptive behaviours and cognitions, and becomes chronic unless treated aggressively in its acute phase. Spielman and colleagues¹³ set forth what has become known as the ‘3-P Model’ of insomnia, which is essentially a diathesis-stress model. The model suggests that (i) individuals may be primed to develop insomnia by individual predisposing characteristics, such as various forms of hyperarousal and/or tendency to worry or ruminate, (ii) precipitating factors, such as stressful life events and/or new illness, initiate an episode, and (iii) predisposing factors, such as maladaptive coping strategies like napping or extending time in bed beyond the usual sleep window despite being asleep less, result in conditioned arousal and chronic insomnia.

Hyperarousal, circadian dysrhythmia, and homeostatic dysregulation of sleep are each thought to contribute to the occurrence of insomnia. The largest body of work exists for hyperarousal conceptualized as either elevated basal levels or as a failure to downregulate at night and further construed along somatic/ physiologic, cognitive, and cortical/neurophysiologic dimensions.¹⁴ In terms of physiologic arousal, patients with insomnia have been shown to have elevations of heart rate, galvanic skin response, sympathetic arousal (as measured by heart rate variability), and increased hypothalamic-pituitary-adrenal (HPA) axis activity. In terms of cognitive arousal, patients with insomnia are more prone to generalized worry, sleep-related worry, and selectively attend to and monitor insomnia symptoms. In terms of cortical/neurophysiologic arousal patients with insomnia exhibit increased high frequency EEG activity at or around sleep onset and during non-rapid eye movement (REM) sleep, elevated whole brain metabolism across

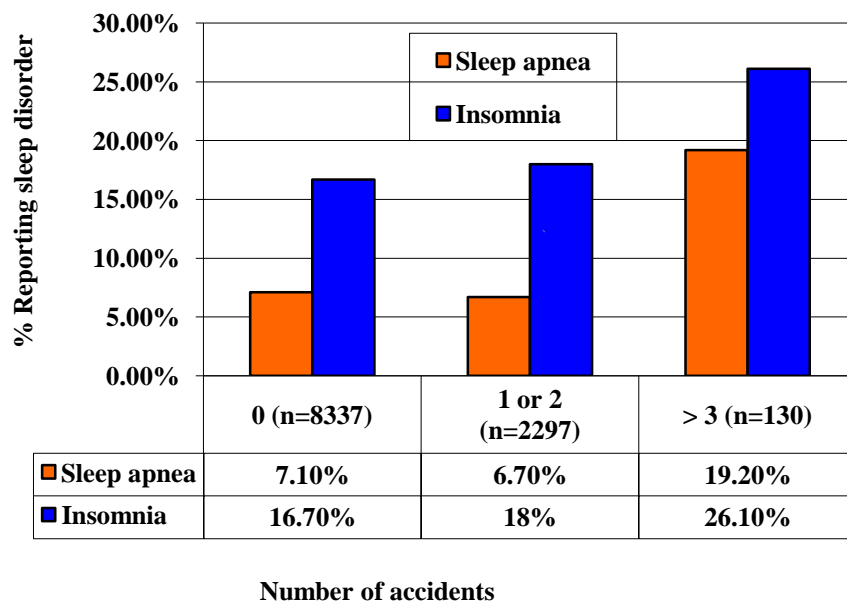
waking and non-REM sleep¹⁵, and smaller metabolic declines than normal in the ascending reticular activating system, in the hippocampus, the amygdala and anterior cingulate cortex during the wake to sleep transition.¹⁶

As far as circadian dysregulation is concerned, research suggests that chronobiologic abnormalities, in the form of phase shifts of the core-body temperature rhythm, are related to sleep initiation or maintenance problems. These shifts are similar to but smaller than those seen in full-fledged circadian rhythm disorders of sleep. It actually reset the “biological clock”. Patients with Primary Insomnia, as compared to good sleepers, tend to exhibit homeostatic abnormalities. First, sleep propensity is measured by the multiple sleep latency test¹⁷ (MSLT) in which mean time to fall asleep across successive daytime napping opportunities represent the level of objective sleepiness or sleep drive. Given that patients with insomnia tend to have less total sleep time than good sleepers, they would be expected to have shorter sleep latencies on the MSLT. Most MSLT studies have shown that patients with insomnia have normal, or longer than normal sleep latencies¹⁸. This suggests a possible reduction in sleep drive, and by inference, a faulty sleep homeostat. Second, patients with insomnia have less slow wave sleep (SWS) than good sleepers, by itself diminished SWS does not directly implicate homeostatic dysregulation. Third, following sleep deprivation patients with insomnia show diminished SWS, a cardinal homeostatic response to sleep loss.

Consequences of insomnia:-

- Worsens psychiatric disorders
- Prolongs medical illnesses
- Reduced quality of life
- Higher absenteeism
- Increased accident risk
- Higher health care costs
- Cognitive impairment

Car accidents and Sleep disorders:-



Economic impact of insomnia:- **Direct Cost**

- Drugs: \$1.97 Billion (41% prescription)
- Services: \$11.96 Billion

 Indirect Costs

- Decreased productivity
- Higher accident rate
- Increased absenteeism
- Increased co-morbidity

 Total Annual Cost: \$30-\$107 billion**Management of insomnia:-**

After evaluating any medical and psychiatric problems, physician's primary goals are to remove or mitigate these underlying problems, to prevent progression from transient to chronic insomnia, and to improve the patient's quality of life. Achieving these goals involves educational, behavioural, and often pharmacologic intervention.

Pharmacotherapeutic Management:-

Until the advent of the non-benzodiazepine hypnotics, the most commonly used agents were benzodiazepines. Currently approved benzodiazepines for the treatment of insomnia are flurazepam, triazolam, quazepam, estazolam, and temazepam. Although, both subjective and objective studies have generally found improvements in sleep maintenance measures, specifically wake time after sleep onset and number of awakenings, with the longer-acting agents like flurazepam, quazepam, and estazolam¹⁹. Their use, however, is also associated with next-day sedation and impaired cognitive and psychomotor function, ataxia, slurred speech, inattention, risk of tolerance, abuse, withdrawal syndrome and dependence following extended use²⁰. So, benzodiazepines have not been satisfying due to these associated side effects. And, these are the major limiting factors for their use.

Over the past years we have observed clinical and scintigraphic improvement in insomnia patients after administration of 10 mg zolpidem with reduced risk of tolerance, dependence and rebound insomnia.

Zolpidem:-

Zolpidem (*N, N*, 6-trimethyl-1,2-[4-methyl-phenyl]imidazo[1,2-a]pyridine-3-acetamide hemitartrate) is a stable, water-soluble, microcrystalline solid with a molecular weight of 392.4 (weight of salt). Its structural formula is shown in Fig 1. The medicinal chemistry program that led to the discovery of zolpidem an Imidazopyridine derivatives has been described by George et al.²¹

The aim of the drug discovery program that led to zolpidem was to identify a non-benzodiazepine compound that would show a rapid-onset, short-duration hypnotic effect and would bind to benzodiazepine (BZ) receptors. Zolpidem has these characteristics²², but during the course of the pharmacological evaluation of the compound it was found that both, its pharmacological profile and its mechanism of action, differed in

potentially significant ways from those of the benzodiazepines themselves.

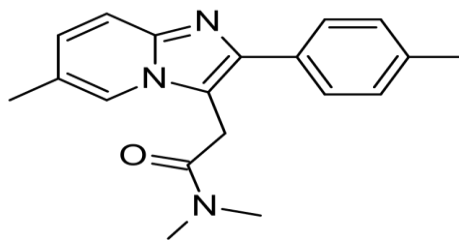


Fig 1: Zolpidem; N, N-dimethyl-2-(6-methyl-2-p-tolylimidazo[1,2-a]pyridin-3-yl) acetamide

Mechanism of action:-

Zolpidem tartrate belongs to the Imidazopyridine group of compounds and is structurally unrelated to other hypnotic agents. Zolpidem tartrate selectively binds the omega-1 receptor subtype (also known as the benzodiazepine-1 subtype) which is the alpha unit of the GABA_A receptor complex. Whereas benzodiazepines non-selectively bind all three omega receptor subtypes, zolpidem tartrate preferentially binds the omega-1 subtype. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem tartrate i.e. the preservation of deep sleep (stage 3 and 4 slow wave sleep).

Pharmacokinetic properties:-

It has both a rapid absorption and onset of hypnotic action. Peak plasma concentration is reached at between 0.5 and 3 hours. Following oral administration, bioavailability is 70% due to a moderate first pass metabolism. The elimination half-life is short, with a mean value of 2.4 hours (+ 0.2 h) and a duration of action of up to 6 hours. Its pharmacokinetic profile is linear in the therapeutic dose range, and is not modified upon repeated administration.

Protein binding amounts to approximately 90%. The volume of distribution in adults is $0.54 \pm$

0.02 L/kg and decreases to 0.34 ± 0.05 L/kg in the very elderly. The main cytochrome P450 enzyme involved in the hepatic biotransformation of zolpidem tartrate is CYP3A4. CYP1A2 and CYP2D6 contribute minimally to the metabolism of zolpidem. All metabolites are pharmacologically inactive and are eliminated in the urine (56%) and in the faeces (37%). Furthermore, they do not interfere with zolpidem tartrate plasma binding. Zolpidem tartrate did not accumulate in young adults following nightly dosing with 20 mg zolpidem tartrate tablets for 2 weeks.

A food-effect study in 30 healthy male volunteers compared the pharmacokinetics of zolpidem tartrate 10 mg when administered while fasting or 20 minutes after a meal. Results demonstrated that with food, mean AUC and C_{max} were decreased by 15% and 25%, respectively, while mean T_{max} was prolonged by 60% (from 1.4 to 2.2 hr). The half-life remained unchanged. These results suggest that, for faster sleep onset, ZOLPIDEM should not be administered with or immediately after a meal.

In the elderly, the recommended dose for ZOLPIDEM is 5 mg. This recommendation is based on several studies

in which the mean C_{max} , $T_{1/2}$ and AUC were significantly increased when compared to results in young adults. Zolpidem tartrate did not accumulate in elderly subjects following nightly oral dosing of 10 mg for 1 week.

Efficacy of zolpidem in Insomnia:-

Zolpidem was first introduced to the market as a short-term treatment for insomnia in France in 1988. It has subsequently been registered in > 70 countries. It was first marketed in the United States in 1993. In some countries, zolpidem is the most widely prescribed and used hypnotic drug. A large number of clinical studies of the efficacy of zolpidem in inducing and maintaining sleep, involving tens of thousands of patients, have been carried out and the results have been published. Several detailed reviews of this literature are available.^{23, 24, 25}

Zolpidem's activity has been evaluated using subjective assessments in which patients responded to questionnaires concerning the latency, quality, and duration of their sleep. In such studies, zolpidem was reported to reduce sleep latency, increase duration, and produce more satisfying sleep. These findings have been confirmed in trials using objective polysomnographic methods in which sleep latency and nocturnal awakenings were reduced and sleep duration was increased. These studies have also reported that sleep architecture was not disrupted during a night of zolpidem-assisted sleep. Analyses of the microstructure of sleep have also been carried out using measures of the cyclic alternating pattern (CAP). CAP rate is significantly correlated with the subjective appreciation of sleep quality even in the absence of significant macrostructural alterations.²⁶ Zolpidem was found to reduce the increased CAP rate shown in the disturbed sleep of insomniac patients and to attenuate the instability of the sleep patterns produced by noise.²⁷ In seeking to develop zolpidem as a rapid-onset, short-duration hypnotic, a major aim was to identify a drug that would not give rise to impairments in performance the day after a night of drug-assisted sleep. Such next-day effects have been a significant cause for concern with some hypnotic barbiturates and benzodiazepines. A number of studies were therefore carried out to investigate next-day alertness and psychomotor performance with zolpidem.²⁸ The results of these studies showed that when appropriate doses of zolpidem (5 to 10 mg) were taken at bedtime there were minimal effects on cognitive or psychomotor performance or daytime drowsiness the next morning.

Safety of zolpidem in Insomnia:-

Before registration and marketing, zolpidem was tested in the appropriate toxicological screens in experimental animals. The results showed that the compound was extremely well tolerated with a large therapeutic ratio.²⁹ In the clinic, controlled trials and postmarketing surveillance have confirmed the positive safety profile.^{30, 31, 32} Zolpidem is also safe in overdose; Garnier et al.³³ reported in a review of 344 cases of intentional, acute overdose that the effects were generally benign, requiring no specific measures except support and perhaps gastric lavage. In post-marketing surveys most reported adverse events were CNS related and not

unexpected for a hypnotic drug (e. g. drowsiness or sedation). Gastrointestinal events such as nausea are also reported occasionally, particularly at higher doses. It has been suggested, in fact, that such effects may limit the abuse potential of zolpidem. Rebound insomnia following cessation of a course of hypnotic treatment, which has been reported to be a problem with some other drugs in this class, is also of minimal significance when zolpidem is used at the correct doses and for an appropriate duration³⁴. It has various advantages over benzodiazepines. Its higher selectivity towards α -1 subunits of the GABA_A receptor can be identified as cause of more specific sleep-related actions and reduction of some undesired adverse effects. Although chronic administration of zolpidem produces neither tolerance to its sedative effects nor signs of withdrawal when the drug is discontinued. Unlike the benzodiazepines, zolpidem has little effect on the stages of sleep in normal human subjects. The drug is as effective as benzodiazepines in shortening sleep latency and prolonging total sleep time in patients with insomnia. After discontinuation of zolpidem, the beneficial effects on sleep reportedly persist for up to 1 week. Tolerance and physical dependence develop only rarely and under unusual circumstances.^{35, 36} Indeed, zolpidem-induced improvement in sleep time of chronic insomnia was sustained during as much as 6 months of treatment without signs of withdrawal or rebound after stopping the drug.³⁷ Nevertheless, zolpidem is approved only for the short-term treatment of insomnia.

CONCLUSION:

Insomnia is the most common sleep disorder. The inability to attain restful sleep in adequate amounts imposes a host of negative consequences. Its impact on financial, social and psychological status of patients and their caregivers cannot be ignored. Moreover, there is large degree of morbidity (medical and psychiatric) that comes with chronic insomnia. Thus finding a novel way to tackle these health problems is the need of present times. Although, Conventional treatment for insomnia includes drugs that exert a depressant effect on the CNS, and psychological therapy. Most of the drugs prescribed for insomnia involve some risk of overdose, tolerance, habituation, and addiction. So, as alternative therapies, zolpidem a novel non-benzodiazepine is an effective option with a reduced risk for dependence in the treatment of insomnia. Zolpidem is less likely to have the drawbacks of conventional drugs. Patients who suffer from longer term insomnia and have predominantly sleep maintenance problems, such as those with psychiatric or medical illnesses, are particularly challenging for clinicians, because little research has been conducted in these patient populations with either behavioural therapy or pharmacotherapy. Although zolpidem is an effective option with reduced risk for tolerance, rebound phenomenon and dependence, and has a positive impact on subjective next-day functioning, more research is needed to improve the therapeutic armamentarium for difficult-to-treat patients as well as to determine the long-term benefits of treating insomnia.

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