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UNDERSTANDING ZOLPIDEM: MECHANISM, PHARMACOKINETICS AND COMPARATIVE ANALYSIS AMONG Z-DRUGS – A COMPREHENSIVE REVIEW

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ABSTRACT

Insomnia is a prevalent medical condition and a major public health concern. In early stages the benzodiazepines are used to treat the insomnia. To address the challenges possessed by traditional benzodiazepine medications, commonly used to treat anxiety and insomnia, non-benzodiazepine hypnotic agents known as z-drugs were introduced in the 1980s. Among these agents, zolpidem stands out as an imidazopyridine hypnotic, selectively binding to the α1 and α5 subunits of the GABA-A receptor, offering a rapid onset and short-duration hypnotic effect. Comparing with other non-benzodiazepines zolpidem has more potential for the treatment of insomnia. Additionally, this article covers the recently developed area of deuterium incorporation in drug design, showing how it can be used to enhance the therapeutic efficacy and pharmacokinetic characteristics of drugs. This comprehensive review offers a thorough summary of the state of insomnia medication today, pointing out the function of zolpidem and the promising prospects for deuterium-based medication growth in addressing the unmet requirements of patients with neurological disorders and sleep disorders.

Keywords: Insomnia, non-benzodiazepine, zolpidem, metabolic pathways, deuterium

INTRODUCTION

Insomnia is one of the most frequent issues in medical practice and a public health concern. Chronic insomnia disorder, short term insomnia disorder and other insomnia disorder comes under the international classification of sleep disorders 3rd edition (ICSD – III). The second edition of international classification of sleep disorder describes various subtypes of insomnia they are psychophysiological insomnia, idiopathic insomnia, paradoxical insomnia, inadequate sleep hygiene, behavioral insomnia of childhood **[1]**. Benzodiazepines are frequently recommended medications used to treat anxiety and insomnia. They are commonly present in drugs like Xanax (alprazolam) and Valium (diazepam) **[2]**. In order to combat some of the drawbacks of benzodiazepines (BZDs), such as daytime drowsiness and following day sedation, z-drugs were first produced in the 1980s for the treatment of insomnia **[3]**. Zopiclone, zolpidem immediate release (IR), zaleplon and eszopiclone **[4]** are non-benzodiazepine hypnotic agent which has an effect in inducing and maintaining sleep in adults **[5]**. Zolpidem is an imidazopyridine hypnotic agent, selectively binds to the α1 and α5 subunits of the GABA a receptor **[6]**. The neuropsychiatric side effects such as delirium, amnesia, hallucinations, sensory distortions, parasomnias or complex sleep behaviours (CSBs), and amnesia all have a connection to zolpidem, according to a number of post marketing studies and case reports **[7]**. If used to treat insomnia, zolpidem extended-release has no added advantages, but it may raise the risk of impairment on the following day **[8]**. Zolpidem also known as N, N-dimethyl-2-[6-methyl-2-94-methylphenylimidazo[1,2-a]pyridine-3-yl]acetamide was the first benzodiazepine receptor created **[9]**. Zolpidem structurally differs from benzodiazepines **[10]** and has minor anxiolytic, myorelaxant, and anticonvulsant properties **[11]**. In therapeutic use, it is the first subtype-specific ligand **[12]**. Summary of zolpidem and the physicochemical characteristics of the drug **[13, 14]** has mentioned in the below **Table 1** and their derivatives [**15]** are listed in **Table 2**. In 1960s, deuterium was included in medicinal molecules based on the isotope effect, deuteration is intended to lengthen the biological activity of medications and enhance their stability because carbon-deuterium (C-D) bonds are more resistant to chemical or enzymatic breakage than carbon-hydrogen (C-H) bonds **[16, 17]**. Deuterium-carbon bond is shorter and 6−10 times more stable than the hydrogen-carbon bond, which makes it hard to break **[18]**.

Table 1: Summary of zolpidem and its physicochemical characteristics

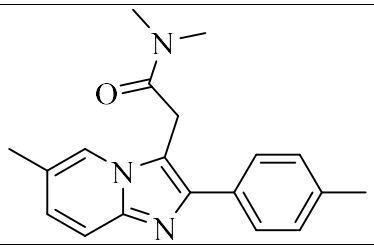
Drug name	Zolpidem
Phase	Launched
Indication	Insomnia
Pharmacology description	Non – benzodiazepine hypnotic, benzodiazepine receptor agonist
Route of administration	Oral
Chemical structure	
Molecular formula	$C_{18}H_{21}N_3O$, ½($C_4H_6O_6$)
Molecular weight	Salt = 392.4 Base = 307.4 Salt/base ratio = 1.24
Melting point	Salt = 193 – 197°C
Appearance	Off – white, microcrystalline solid
Solubility	Salt = 23 mg/Ml in water at 20°C. Base = insoluble in water.
Stability	The chemical is stable to heat, light, and aqueous solutions with pH levels ranging from 1.5 to 7.4 when it is in crystalline form.
Physicochemical characteristics	A saturated aqueous solution's pH value is 4.2. pK_a = 6.16 Log P = 2.42[a]

Table 2: Zolpidem and it's derivatives

Generic name	Trade name	Dose	Indication
Zolpidem	Ambien	5mg, 10mg	*SOI
Zolpidem SL	Edluar	5mg, 10mg	SOI
Zolpidem SL	Intermezzo	1.75mg, 3.5mg	**SMI
Zolpidem oral spray	Zolpimist	5mg, 10mg	SOI
*SOI – sleep onset insomnia, **SMI - Maintenance of Sleep Insomnia characterised by rising in the middle of the night and difficulties returning to sleep [15].			

MECHANISM OF ACTION

Zolpidem is a non-benzodiazepine compound which has a rapid onset, short-duration hypnotic effect by binding to the benzodiazepine receptors [**8**]. Mechanism of action of zolpidem is similar to benzodiazepines BZs [**19**]. Gamma-amino butyric acid (GABA) is a receptor chloride channel modulator that enhances the GABA inhibitory effect, which causes sedation. $GABA_A$, $GABA_B$, and $GABA_C$ are number of subclasses of GABA receptors [**20**]. Benzodiazepines binding sites are associated with $GABA_A$ subtype receptor. $GABA_A$ receptor contains five subunits for the inhibitory neurotransmitter GABA. Low concentrations of zolpidem potentiating the effects of GABA show that it best binds to BZ (α) receptors with subunit 1. For receptors containing the α2 and α3 subunits, larger zolpidem concentrations are necessary to enhance the actions of GABA.

α5 containing receptors show minimal to no response **[8]**. Interaction of GABA appears between the sites of α and β subunits, once the GABA binded with GABAA receptor **[20]**. It is more likely that the frequency of Cl ion channel opening will occur when benzodiazepines and Z-drugs allosterically modify $GABA_A$ receptors **[21]** and the entry of this chloride ion into the cell membrane leads to hyperpolarization **[20]**.

PHARMACOKINETIC PROPERTIES

Absorption:

The oral use of zolpidem results in good absorption. The medication has a 70% oral bioavailability and travels via first-pass metabolism. Administration of drug dose ranges from 5mg to 10mg per day before going to bed. After approximately 1.5 hours following delivery, peak plasma concentrations of 30-250 ng/mL are attained. 92%of zolpidem bounds to plasma protein **[22]**. Six food-effect studies have revealed a more rapid onset of sleep when zolpidem is administered right after a meal **[8]**.

Distribution:

Zolpidem distribution study has conducted in rat by autoradiography method **[23]**. Initially, the medication was distributed evenly throughout the body, with the lowest amounts in the CNS and the greatest in glandular tissues and fat **[5]**. Zolpidem crosses the blood brain barrier rapidly. Volume of distribution in animals ranges from 0.9 to 1.6 L-kg-1 and approximately 0.54L-kg-1 in man **[23]**. In rats, the brain or plasma concentration ratio was 0.3 to 0.5, with unaltered medication accounting for 40 to 90% of radioactivity in the CNS **[5]**. After 3 hours, zolpidem was excreted in the milk in amounts ranging from 0.76 to 3.88 µg, which corresponded to 0.004 to 0.019% of the dosage that was given; no measurable amounts (below 0.5 ng/ml) of zolpidem were discovered in the milk at any further sample intervals **[24]**.

Metabolism:

Zolpidem is highly metabolized, and three primary metabolites have been identified in humans, although none of these seem to have any discernible pharmacological effects [**25]**. After oral or intravenous administration, the amount of zolpidem that has been unchangedly eliminated in urine is under 1%., indicating that clearance is essentially metabolic **[26]**. In circulation, it binds to both albumin and α1 acid glycoprotein **[27]**. Human cytochrome P450 (CYP) enzymes substantially metabolize zolpidem into inactive metabolites, particularly CYP3A4 (61%) [**26]**. Other metabolic enzymes include 22% for CYP2C9, 14% for CYP1A2, 2.5% for CYP2D6, and 0.5% for CYP2C19 **[19]**. In zolpidem the major metabolic routes are oxidation and hydroxylation **[8]**. In human biotransformation occurs via different pathways **[19]** which is mentioned in **Figure**

1. Methyl oxidation on phenyl ring moiety and imidazopyridine ring moiety leads to formation of alcohol to carboxylic acid derivative this is the main major metabolic route and hydroxylation occurs in another position of the imidazopyridine ring moiety **[25]**. Most of the dosage gets eliminated as metabolites in the bile, urine, and faeces **[26]**.

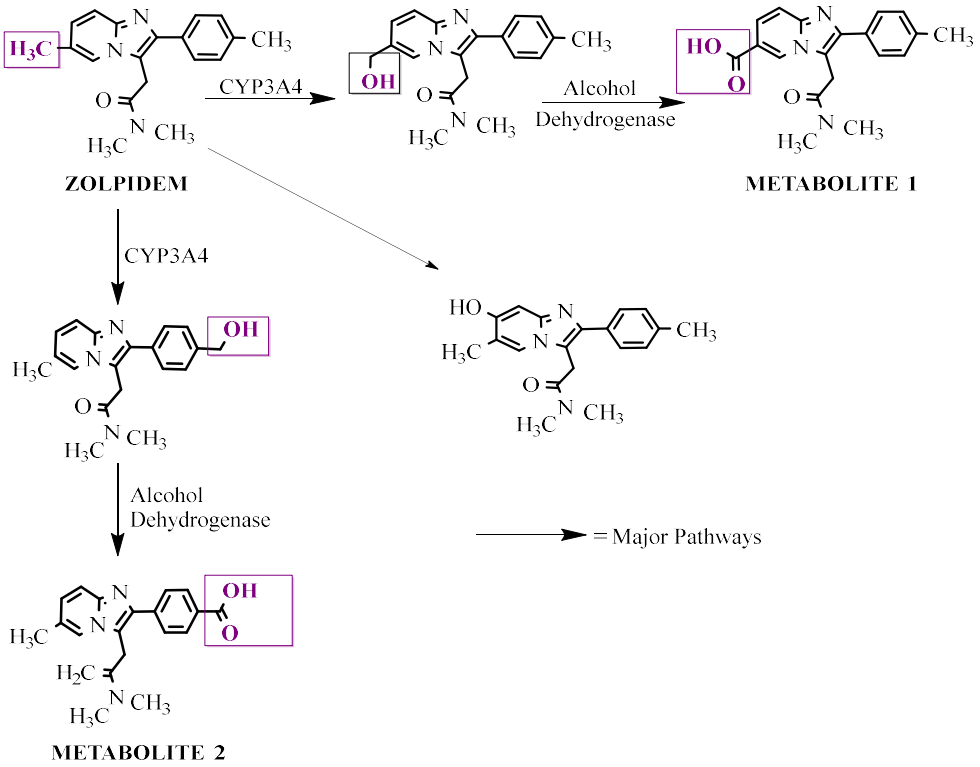


Figure 1: Metabolic pathways of zolpidem

TOLERANCE, DEPENDANCE AND WITHDRAWAL

In just a few weeks, some persons can become tolerant to the effects of zolpidem **[29]**. Treatment for zolpidem tolerance and physical dependency often involves a progressive dosage reduction over several months to reduce withdrawal symptoms **[30]**. Despite the lack of a definitive term, zolpidem dependent syndrome must be recognised. High dosages, the patient's psychiatric condition, and manipulative actions, such as lying to get a bigger supply of the drug, should warn doctors **[31]**. 2014 review identified addiction to drug, knowing that zolpidem is found in 20% of fake or fraudulent prescriptions in France, there is now an official warning on this medication **[32]**. However in primates, tolerance equivalent to that of benzodiazepines was detected. In rodent studies, zolpidem has

been shown to have a lesser tendency for tolerance than benzodiazepines **[33]**.

COMPARISON OF ZOLPIDEM WITH OTHER Z-DRUGS: ZALEPLON, ZOPICLONE AND ESZOPICLONE DRUGS

Zaleplon is a pyrazolopyrimidine hypnotic drug. According to the biopharmaceutical classification system, Zaleplon is classified as a Class II medication due to its weak solubility and high permeability, which is responsible for the slow rate of dissolution, delayed onset of action, and constrained absorption **[34]**. Zaleplon undergoes significant first-pass metabolism, which is responsible for its poor bioavailability (30%) **[35]**. Because of the high dose of Zaleplon, one of its main disadvantages was hallucination **[34]**. Zaleplon, a non - benzodiazepine hypnotic, may potentially be used in teenagers with delayed sleep-phase syndrome since it has a rapid beginning of action and its hypnotic effects should wear out long before the required wakeup time **[36]**. Zaleplon undergoes three inactive biotransformation's in vivo. Zaleplon is biotransformed in vitro via CYP3A4 and cytosolic aldehyde oxidase, with CYP1A2 and CYP2D6 potentially playing supporting roles **[37]**. Out of these three, zaleplon has the shortest half-life, lasting an hour, whereas zolpidem and eszopiclone have half-lives of 1.4–4.5 hours and 6 hours, respectively **[38]**.

Eszopiclone (Lunesta, Sunovion) is an authorised non-BZD hypnotic medication for the long-term management of insomnia. CYP3A4 is the primary metabolizer of eszopiclone **[39]**. Eszopiclone, a racemic zopiclone's dextrorotatory enantiomer, features a single chiral centre with a S(+)-configuration **[40]**. According to the EC50 data, racemic zopiclone is most active at the α1 and α5 receptors, with efficacy equivalent to zolpidem at the α1 receptor, whereas eszopiclone is most potent at the α5 receptor, followed by the α2 and α3 receptors, and is least potent at the α1 receptor. Eszopiclone, for instance, has a potency of one that is 3.4 times lower than zolpidem. The variations seen between the two hypnotics might be explained by the different ways that racemic zopiclone and eszopiclone affect GABA -subunits. For instance, eszopiclone may be less harmful to memory than zopiclone due to the efficacy at the α5 and α1 subunits being reduced compared to the various units. Additionally, it could have stronger anti-depressive effects and anxiety-lowering effects than zopiclone because high efficacy at the α3 and α4 subunits being higher than the other units **[41]**. Eszopiclone undergoes substantial oxidative and demethylative metabolism in the liver. The binding potency of the major plasma metabolites to GABA receptors is low to nil. Eszopiclone is metabolized by the enzymes CYP3A4 and

CYP2E1, according to in vitro research **[38]**. Zopiclone is a cyclopyrrolone chemically **[42]**. Zopiclone, a drug that is structurally unrelated to benzodiazepines, has a pharmacological profile that is comparable to benzodiazepines in animals **[43]**. It increases GABA-related neuronal inhibition because it is a kind of A –amino butyric acid (GABA) receptor agonist **[44]**. There are two main metabolites one is N-desmethyl-zopiclone which is inactive and the other is zopiclone N-oxide which is weakly active **[41]**. Principle of zolpidem and other z-drugs properties are mentioned in **Table 3**.

Table 3: Principle of Z-drug and it's properties

Drug name	Metabolism	Onset (min)	Half life	Duration of action	Insomnia indication	Adverse effect
Zolpidem	Metabolism occurs by methyl oxidation on phenyl ring and imidazopyridine ring.	30	1.4-4.5	Short	Start of sleep	Drowsiness, dizziness, diarrhoea.
Zolpidem ER		30	1.5-5.5	Intermedia te	Start of sleep and sleep maintenance	
Zaleplon	It is primarily metabolized by aldehyde oxidase.	20	0.5-1	Ultra short	Start of sleep	Headache, dizziness, drowsiness, nausea, abdominal pain, memory impairment.
Eszopiclone	It is significantly metabolised in the liver by oxidation and demethylation.	30	6-7	Intermedia te	Maintenance sleep	Headache, unpleasant taste, somnolence.
ER-Extended release. Zaleplon has a shorter half-life, so it does not show up the next day; if needed, it may be administered within 4 to 5 hours after waking up without the danger of a hangover the next day. [19,34,39,45].						

OFF-LABEL USE OF ZOLPIDEM

Dystonia is a hyperkinetic motion condition that causes abnormal, frequently repeated, movement's postures, or both. The movements are usually patterned, twisting, and tremulous [**46]**. According to reports, the imidazopyridine agonist zolpidem, which has a strong affinity to the benzodiazepine subtype receptor BZ1, can treat several kinds of dystonia and diseases of the basal ganglia, including Parkinson's disease When oral medicines or botulinum toxin are ineffective for treating generalized/hand dystonias and Meige syndrome, zolpidem may be an effective alternative [**12]**. In a double-blinded, placebo-controlled research, ten Parkinson's disease patients showed a reduction of 30.2% on the Unifying Parkinson's Disease Rating Scale for one hour after receiving only one oral dosage (10 mg) of zolpidem [**47]**. Postoperative pediatric cerebellar mutism syndrome (pCMS) is one of the therapeutic settings in which zolpidem treatment has encouraged unexpected recovery. A serious pediatric postoperative complication known as pCMS can develope, especially after the removal of a

medulloblastoma (MB) [**48]**. Improvements in arousal and motor function, particularly in different stages of consciousness (DOCs) and movement disorders, have been seen when zolpidem is used to treat a range of neurologic conditions [**49]**. When electroconvulsive therapy and benzodiazepines failed to help catatonic patients regain consciousness, zolpidem appears to be a safe and successful treatment. Symptoms of catatonia improved when plasma zolpidem levels were between 80 and 130 ng/L. This impact began 15 minutes after zolpidem administration and persisted for around 2 to 5 hours [**50]**. In an instance of traumatic brain injury, zolpidem showed brief paradoxical improvements in a patient with neurological deficits [**51]**. Tuberculosis (TB), a chronic granulomatous disease caused by Mycobacterium tuberculosis (M. tuberculosis), is one of the most common infectious infections. This aerosol-based infectious disease is one of the most serious infectious diseases in the world [**52]**. Imidazo[1,2-a]pyridines have inherent in vitro potency, selectivity, and low toxicity, as demonstrated by the rational redesign of the structural moieties present in zolpidem, which gives access to exceptionally potent antituberculosis compounds (MICs as low as 0.004 μM) [**53]**.

DEUTERIUM INCORPORATED DRUGS

Tetrabenazine (TBZ) was the first medication to get FDA clearance for the management of Huntington's disease and it remained the only medication with this indication until deutetrabenazine was certified in 2017 [**54]**. Huntington's disease (HD) is an autosomal ailment characterised by progressive neurological disorder due to misfolded proteins, resulting from a mutation in a single gene [**55]**. Tetrabenazine is a medication that comes in a deuterated version called deutetrabenazine [**54]**. TBZ has a half-life of 5-7 hours administered three times daily, deutetrabenazine allows for twice-daily dosage and has an approximate 9-10 hour half-life, without a rise in the peak plasma levels of active metabolites [**54, 56]**. The primary symptomatic treatment for Parkinson's disease continues to be L-3,4-dihydroxyphenylalanine (L-DOPA), the precursor to dopamine (DA), together with a peripheral DOPA decarboxylase (DDC) inhibitor. The specific sites for deuterium replacement were selectively based on previously demonstrated slower oxidative deamination of DA by monoamine oxidase (MAO) and slower the production of norepinephrine by dopamine β-hydroxylase (DBH), when deuterium is introduced at the α-carbon and β-carbon. Targeted deuteration in α and β locations of the L-DOPA side chain reduces the metabolic

breakdown of dopamine DA by monoamine oxidase MAO [**57]**.

CONCLUSION

To address the drawbacks of benzodiazepines (BZDs) in treating insomnia, non-benzodiazepine hypnotic agent, particularly zolpidem, zopiclone, zaleplon, and eszopiclone have emerged as effective alternatives. Comparisons between zolpidem and other non-benzodiazepine hypnotics, namely zaleplon and eszopiclone, highlight differences in absorption, metabolism and elimination half-life. One important aspect to consider is zolpidem get metabolized easily and has short duration of action. To increase the metabolism deuterium, comes as a novel approach. The phenyl ring and imidazopyridine ring are possible sites for Deuteration. This review gives detailed updated information about the drug zolpidem and we conclude that deuteration can be a possible approach to further enhance the action of zolpidem.

CONFLICT: No conflict of interest.

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