

ZOLPIDEM



“The Lovers”, oil on canvas, 1928, Rene Magritte

“....When one see one of my pictures, one asks oneself this simple question, “What does it mean?” It does not mean anything, because mystery means nothing either, it is unknowable”

Rene Magritte

One of the most plagiarized artists, the surrealist painter Rene Magritte (1898 - 1967) attracted great acclaim during and after his lifetime with his individual, witty and thought-provoking images.

Faces covered with cloths often appear in Magritte's paintings. Frustrated desires are also a common theme. Here, two figures have their heads enshrouded with white cloths and yet they kiss through them. As in Klimt's painting, "The Kiss", the man leans down to the woman and she tilts her head towards him, but, unlike Klimt's painting this intimate moment is disturbing. With no windows and depicted in dull colours the room around the two figures seems claustrophobic. The man wears a black suit and tie with a white shirt, the woman wears a red, sleeveless garment with white trim - smart clothes that add further ambiguity. It was the first in a series of four versions of this theme that Magritte painted in 1928, and which remains enigmatic as Magritte evaded explanations, saying they diffused the mystery of his images. His naturalistic style deliberately aimed to present the darker side of the unconscious mind.

Susie Hodge, "The Short Story of Art", 2017.

In the late Nineteenth century Sigmund Freud expounded the strong view that the mind operated on three distinct levels. Our conscious mind, he wrote, is our immediate awareness of the world around us, and yet this part of the mind was merely the tip of a large iceberg. Below the surface lay the preconscious containing all our stored memories and accumulated knowledge, which could be drawn upon as required. But deeper again to this level lay a vast unconscious realm largely inaccessible to the conscious mind, that consisted of the accumulated primal instincts of untold eons of evolution. The subconscious without our being aware of it, influenced everything that we thought, and felt, judgment, feelings, desires, emotions, fears, instincts. The subconscious was the ultimate source of all human behaviour and as such to unlock its secrets would be to understand human behaviour. Freud believed that dreams were the conscious mind's way of accessing the subconscious. To understand what a person's dreams were saying would therefore be to understand the person at the most fundamental level. Freud believed that dreams were truthful manifestations of unconscious fears and desires. His ideas were extremely influential in the late Nineteenth and early to mid-Twentieth century and became the manifesto of the brilliant Surrealist artists, who strove to depict the subconscious mind on canvas.

Magritte's "The Lovers" is a quintessential work of mid-Twentieth century Surrealism. He never explained its meaning, nor any of his other works for that matter, preferring to let the viewer assign their own meaning to them. His works therefore necessarily evoke different "meanings" to different people, according to the hard wiring of their own unconscious minds. Nonetheless Magritte's works often strike universal chords of the human condition. "The Lovers" evoke, imagined, unobtainable, forbidden, disturbing, repressed or even taboo desires. The figures kiss, but only their suppressed subconscious, understands just exactly who it is they are kissing!

Surrealist type Art was not necessarily an invention of the Twentieth, century. The works of Hieronymus Bosch or Pieter Bruegel for example could be described as medieval versions of Surrealism. Previous ages assigned such Art to divine inspiration or more sinisterly to Satanic inspiration. The Surrealists assigned their works to the unconscious mind. Modern psycho-pharmacology seeks to suppress subconscious maladies, however with some drugs poorly understood, such as zolpidem, rather than suppress the subconscious, they may unleash it!

ZOLPIDEM

Introduction

Zolpidem (trade name in Australia “**Stilnox**”, among many others) is a controversial hypnotic agent used for the short term treatment of insomnia.

It is a non-benzodiazepine GABA agonist that was introduced as an agent to treat insomnia. When introduced it was said to have the advantages of causing less morning sedation and less disruptive effects on normal sleep patterns, (eTG Complete, November 2011)

Subsequent experience however does not seem to have supported these claims.

In May 2013, the FDA specified new dosage recommendations for zolpidem because of concerns regarding next-morning impairment and a number of high profile media reports from Australia have suggested that, at least in a small number of cases, paradoxical and bizarre sleep disturbances may occur.

In February 2008 the Australian TGA put out the following warning:

- Zolpidem may be associated with potentially dangerous complex sleep-related behaviours which may include sleep walking, sleep driving and other bizarre behaviours. Zolpidem is not to be taken with alcohol.

Caution is needed with other CNS depressant drugs. Limit use to four weeks maximum under close medical supervision.

The effects of zolpidem are reversed by the benzodiazepine antagonist **flumazenil**.

See also separate documents on:

- **Insomnia (in Clinical Presentations folder)**
- **Flumazenil (in Drugs folder)**

History

In Australia zolpidem has been the subject of a number of high profile media stories related to its alleged ability to cause bizarre behaviour.

In 2007 it received widespread media coverage after the death of death of Mairead Costigan, a philosophy graduate who died after falling from the Sydney Harbour Bridge during what her family claims was a stilnox-influenced sleepwalking event.

In 2010 a young Melbourne woman Phoebe Handsjuk fell to her death after allegedly climbing into in a twelfth-floor garbage chute. The Victorian coroner ruled it was an accident whilst under the influence of alcohol and stilnox.

In 2014 Australian Olympic gold medal champion Grant Hackett was admitted to a rehab unit in the United States because of a dependency on Stilnox.

In May 2013, the FDA specified new dosage recommendations for zolpidem because of concerns regarding next-morning impairment

Chemistry

Zolpidem belongs to the **imidazopyridine** group of compounds and is *structurally unrelated* to other hypnotic agents.

Classification

Zolpidem belongs to a novel class of non-benzodiazepine GABA agonists that target subunits of the **GABA-A** receptor complex.

The pharmacodynamics of these agents are very similar to the classical benzodiazepine drugs and therefore show similar therapeutic effects, side-effects, and adverse reactions.

However, non-benzodiazepine GABA agonists have dissimilar or entirely different chemical structures and are therefore unrelated to the benzodiazepines on a molecular level, (see **Appendix 1 below**).

Non-benzodiazepine GABA agonists currently include:

1. Imidazopyridines:
 - **Zolpidem**
2. Cyclopyrrolones:
 - Zopiclone
3. Pyrazolopyrimidines
 - None in current clinical use in Australia

Preparations

Zolpidem titrate as:

Standard release:

- 10 mg

Controlled release:

These tablets should be swallowed whole and not do not crushed or chewed.

- 6.25 mg
- 12.5 mg

Mechanism of Action

Zolpidem 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 **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, i.e. the preservation of deep sleep (stage 3 and 4 slow wave sleep).

Pharmacodynamics

Controlled release tablets may provide a longer sleep period

Zolpidem, generally preserves the normal stages of sleep.

Pharmacokinetics

Absorption:

- Zolpidem is administered orally
There is rapid and almost complete absorption from the GI tract
- The absolute bioavailability is around 70%
- Peak plasma concentrations are reached at between 1.5 - 2.5 hours.

Distribution

- The in vitro plasma protein binding is around 92%.
- The distribution volume in adults is 0.54 L/kg following *intravenous* administration.
- Zolpidem is excreted into human breast milk in small amounts.
- Human placental transfer can occur

Metabolism and excretion:

- Zolpidem is metabolized by the cytochrome P450 enzyme system, principally by CYP-3A4.

All metabolites are pharmacologically inactive and are eliminated in the urine (60%) and in the faeces (40%).

Indications

The primary indication for zolpidem is the *short-term* treatment of **insomnia** in adults.

Use should be limited to a maximum of four weeks under close medical supervision.

Use the **lowest** possible dose **short term** only **dependence, tolerance** and **misuse** comparable to benzodiazepines can occur.

A withdrawal syndrome may also occur on stopping treatment, particularly if taking high doses.

Contra-indications/precautions

These include:

1. Concomitant alcohol intake:
 - Contraindicated (increases the risk of dangerous behaviours, e.g. sleepwalking).
2. Drug or alcohol misuse or psychiatric disorders increases the risk of dependence.
3. Depression, psychosis or schizophrenia

Zolpidem is not recommended as primary therapy in patients with depression or psychosis:

- May worsen these conditions (including the risk of **suicide**)
 - In addition, combining zolpidem with **drugs** used to treat these conditions may also increase the likelihood of dangerous sleep behaviours, e.g. sleepwalking.
4. As with all CNS depressants, there is potentiation of CNS depressing effects when these are used in combination.
 5. Elderly
 - Elderly are more sensitive to adverse effects. Use lower doses.

6. Hepatic impairment:
 - In patients with hepatic impairment, the clearance of zolpidem is decreased and the elimination half-life is extended (around 10 hours).
7. Sleep apnoea.
8. Myasthenia gravis.
9. Chronic lung disease
10. Contraindicated in children < 18 years

Pregnancy

Zolpidem is classified as a category B3 drug with respect to pregnancy.

Category B3 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

There is limited safety information available following the use of zolpidem during pregnancy.

Most studies have shown that there is no significant increased risk of fetal malformations following maternal use of zolpidem.

However, there have been two case reports of intestinal malformations following maternal zolpidem use.

Infants exposed to zolpidem in utero may also be at an increased risk of preterm birth, low birth weight and neonatal withdrawal symptoms.

Additionally, a single case report of high dose maternal zolpidem intake (100mg daily) inducing fetal neural tube defects has been described.

Therefore, consider an alternative medicine with a greater safety profile compared to zolpidem for the management of insomnia during pregnancy.

Non-drug treatments should also be employed.

If zolpidem is the medicine of choice, use the lowest effective dose for the shortest duration possible.

Inform neonatal care providers regarding maternal use to zolpidem and observe the infant for adverse effects or withdrawal symptoms.

There is still a lack of information on long term behavioural and cognitive outcomes among infants exposed to zolpidem in utero.

Breast feeding

Small amounts of zolpidem are excreted into breast milk, but these amounts are unlikely to pose harmful effects to the breastfed infant (8).

In women who choose to breastfeed their healthy full-term infant while taking zolpidem, closely observe the breastfed infant for adverse effects such as drowsiness, poor feeding and sleeping pattern changes. Inform neonatal care providers immediately if any adverse effects are noted in the breastfed infant.

There is still a lack of information regarding the neuro-developmental outcomes of infants exposed to zolpidem via breast milk.

Adverse Effects

These include:

1. Sedation
 - Including, next morning drowsiness, if used in excessive doses.
2. Hallucinations
3. Amnesia:
 - As with most sedative/ hypnotic agents zolpidem may induce anterograde amnesia.

The condition occurs most often several hours after ingestion, therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of around 7-8 hours.
4. As for the benzodiazepines in general, effects are potentiated with alcohol and other CNS depressant agents.
5. Sleep disorders:

Zolpidem may be associated with potentially dangerous **complex** and **bizarre** sleep related behaviours, with subsequent amnesia for these events. Reported reactions include:

- Nightmares
 - Sleep walking
 - Sleep driving, (particularly dangerous, if this actually exists!)
 - Preparing and eating food
 - Making phone calls/ texts
 - Having sex.
6. Paradoxical symptoms of hyper-activity:
- Worsening insomnia
 - Irritability/ agitation
 - Acute rage/ aggression.
7. Hepatotoxicity (rare)
8. Addiction, tolerance and withdrawal symptoms:
- As for the benzodiazepines; addiction, tolerance and withdrawal symptoms can all occur with zolpidem use.
 - Continuous long term use of zolpidem is **not** recommended and should not exceed **four weeks**.

Dosing

Use should be limited to a maximum of four under close medical supervision.

Usual adult dosing is:

- Conventional tablet, oral:
 - ♥ Initially 5 mg immediately before bed; if necessary, increase to 10 mg
- Controlled release tablet:
 - ♥ Oral, initially 6.25 mg immediately before bed; if necessary, increase to 12.5 mg

For dosing in the elderly or those with mild to moderate hepatic impairment

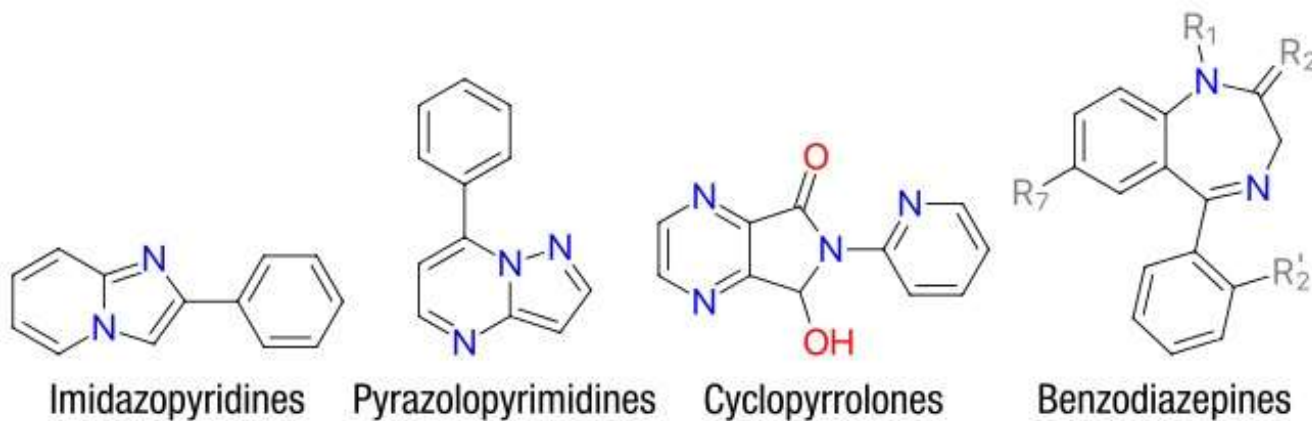
- Conventional tablet, oral 5 mg immediately before bed.

- Controlled release tablet, oral 6.25 mg immediately before bed.

Reversal of effects:

The effects of zolpidem are reversed by the benzodiazepine antagonist **flumazenil**.

Appendix 1



Core structures of 3 non-benzodiazepine GABA agonists in comparison to the core structure of the benzodiazepines.

References

1. eTG - March 2017.
2. Zolpidem in Australian Medicine's Handbook Website, Accessed May 2017.
3. Zolpidem in MIMs Website, 1 April 2017.
4. Zolpidem in RWH Pregnancy and Breastfeeding Guidelines, 19 July 2016

Dr J. Hayes
August 2017.