THE NORTHERN HOSPITAL

ZOPICLONE

"Object", (or "Surrealist Object" or "Breakfast in Fur") Gazelle pelt covered cup, saucer, and spoon, 1936. Meret Oppenheim, Museum of Modern Art, New York.

"Ah this eternal Fur-cup! You make an object, which gets placed on an altar, and everybody only speaks of it and nothing else...

I despise labels. Above all, I reject the term "Surrealist" because it has not had the same meaning since the Second World War as it did earlier. I believe what Breton wrote about poetry and art in his first manifesto in 1924 were some of the most beautiful words to have been written on the subject. By contrast, I feel quite sick when I think of all the things making reference to Surrealism today"

Meret Oppenheim, 1984

The most enigmatic and radical Art genre of the Twentieth century was Surrealism, an attempt to capture the essence of the subconscious mind. Today it is often falsely considered to have been a purely visual Art that was produced by famous males, such as Max Ernst, Rene Magritte and Salvador Dali. But this image is false. Surrealism was more than simply painting, it was a whole philosophy of looking at life, that involved not only painting but also literature, photography and sculpture. Further it was a genre that many supremely talented women engaged in, including Eileen Agar, Leonora Carrington, Leonor Fini and Dorothea Tanning. All these women were very famous Surrealists in their day, but it was the Swiss-German, classical 40s beauty, Meret Oppenheim who produced one of the most famous icons of Surrealist sculpture, and her fame today rests largely on this single work, known simply as "Object", 1936. This fact distressed her when reminiscing in 1984, just a year before her death. "Ah this eternal Fur-cup!", she once exclaimed. "You make an object, which gets placed on an altar, and everybody only speaks of it and nothing else!"

The "official" founder of Surrealism André Breton argued that mundane things presented in unexpected ways had a powerful ability to challenge and disturb reason, and by so doing forced individuals to connect with their subconscious, whether they were ready for it or not. With "Object" this is precisely what Meret Oppenheim achieved. The writer and Surrealist, Desmond Morris, indeed ranked this work alongside Salvador Dali's soft watches and Marcel Duchamp's urinal-fountain as one of the three most iconic images of Surrealism produced in the Twentieth century. And the whole work started out as a complete joke! Early in 1936, Meret was having a morning coffee in a Parisian café with Pablo Picasso and his then partner and muse, Dora Maar. She was a striking woman, made even more so by her sense of the unusual and bizarre and Picasso was totally entranced by her. He noticed Meret's wrist bracelet, one that she had designed herself. It was made of metal but was lined by fur. Jokingly he commented that it seemed "one could cover anything with fur". Meret picked up her cup and saucer and quipped, "Oh, even this cup and saucer?" "Waiter, a little more fur please!", she then called out.

She could not get the idea out of her head and after leaving the café she went straight to a Uniprix department store where she bought a cup, saucer and spoon which she then carefully lined with the fur pelt of a gazelle. This disconcerting work which she simply called "Object", so caught the imagination of the Surrealists that she was invited to exhibit it at the Charles Ratton Gallery in Paris, where it caused a sensation. Later in the year "Object" was sent across the channel to London to appear in the International Surrealist Exhibition in June. Eventually it was bought by the Museum of Modern Art in New York. If mundane things presented in unexpected ways can powerfully challenge and disturb reason, then Meret's "Object" had certainly hit the mark as a powerful icon of Surrealism which aimed to crack the thin veneer of civilized society, revealing the sexual, psychological, and emotional drives burning just beneath the surface. Meret had transformed an item traditionally associated with decorum and feminine refinement into a confounding Surrealist sculpture, that for many who saw it, held unsettling connotations. "Art…has to do with spirit, not with decoration," Meret once wrote. "Object" or the "furry teacup" as it affectionately became known to the public, evoked just such an unsettling mix of connotations. The teacup itself may represent manners, refinement and civilization, but the pelt fur suggests the very opposite - the raw wild animal of nature. With its fur the teacup becomes soft, rounded, and highly tactile, one

cannot help imagining drinking from it - the physical sensation of warm wet fur filling the mouth is quite unsettling. Indeed the idea of actually drinking from it was so disturbing that it became indelibly lodged into the public psyche. For many commentators - both then and today, - "Object" had "undoubted" hidden erotic undertones.

To male Surrealists of the mid-Twentieth century women were often not taken seriously in an artistic sense, rather they were usually stereotyped as secondary figures as muses, decorative items or simply as sexual outlets. Indeed there were a number of Surrealist "groupies" who did fit this role, but this was not for Meret Oppenheim at all, who was an early feminist and wanted to be known for her work not as a "female Surrealist", but simply as a Surrealist. And yet to gain acceptance into this exotic avant-garde world she often nonetheless submitted to the stereotypical role of Surrealist "muse". Like Lee Miller, she first came to prominence as a model of the Surrealist photographer Man Ray. In 1933 Ray photographed her in a series standing next to a large printing press machine, stark naked, apart from a long line of painter's ink running down the underside of her left arm and forearm. Her dark hair is cropped very short, her face unsmiling, and totally expressionless. She appears as if a victim of some unidentified ritual, in which the heavy machinery seems to be menacing her in some unspecified way. The meaning is unclear - but at the same time disturbing - a perfect work of dark Surrealism. Many years later when she was asked of her opinion of her male Surrealist colleagues, she simply replied that they were all a "bunch of bastards".

The agent zopiclone is often mistakenly taken for an everyday benzodiazepine, but this is not true. Though it does act as a GABA agonist it is much more Surrealist than this! Its mundane appearance may for some conceal an array of disturbing unexplained adverse reactions in the form of complex and bizarre sleep related behaviours - a startling release of the subconscious mind!

Meret Oppenheim, 1943, (photographer unknown).

ZOPICLONE

Introduction

Zopiclone is a non-benzodiazepine GABA agonist.

It is used primarily as a short-acting hypnotic agent for the short term (**2 - 4 weeks**) 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).

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

See also separate documents on:

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

History

Zopiclone was developed in 1986

Chemistry

Zopiclone, a cyclopyrrolone derivative.

It belongs to a novel chemical class which is structurally unrelated to other existing hypnotics, though its pharmacological profile is similar to that of the benzodiazepines.

Classification

Zopiclone 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

Zopiclone as:

Tablets:

- 7.5 mg.

Mechanism of Action

Zopiclone 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**, zopiclone **preferentially binds the omega-1 subtype**.

Pharmacodynamics

Zopiclone reduces sleep latency, increases the duration of sleep and decreases the number of nocturnal awakenings.

Zopiclone delays the onset of rapid eye movement (REM) sleep but does not reduce consistently the total duration of REM periods.

The duration of stage 1 sleep is shortened and the time spent in stage 2 sleep is increased.

In most studies, stage 3 and 4 sleep tend to be increased, but no change and decreases have also been observed.

The effect of zopiclone on stage 3 and 4 sleep differs from that of the benzodiazepines, which suppress slow wave sleep. The clinical significance of this finding is not known.

Pharmacokinetics

Absorption:

- Zopiclone is administered orally.

- Bioavailability of the 7.5 mg tablet is around 75 % due to first pass metabolism.

Distribution

- Protein binding is around 45 %.
- Zopiclone crosses the human placenta
- Zopiclone is excreted into human breast milk in small amounts.

Metabolism and excretion:

- Zopiclone is extensively and rapidly metabolized by the liver. A large number of metabolites have been isolated.

  The N-oxide analogue has weak pharmacological activity.
- The volume of distribution of zopiclone averages around 104 liters.
- The half-life of zopiclone is around 4.5 - 6 hours; and for its main metabolite around 4 - 5 hours.

Indications

Zopiclone is indicated for the short term treatment of insomnia (**2 - 4 weeks**).

Contra-indications/precautions

These include:

1. Known hypersensitivity to zopiclone
2. Concomitant use of other CNS depressants
   - Including alcohol.
3. Myasthenia gravis.
4. Severe impairment of respiratory function.
   - Including sleep apnoea
5. Severe hepatic insufficiency.
6. Contraindicated in children.
7. Elderly:
   - More sensitive to adverse effects.

Pregnancy

Zopiclone is a category C class drug with respect to pregnancy

Category C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

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

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

Women exposed to zopiclone during pregnancy may be at an increased risk of a preterm birth, low birth weight and neonatal withdrawal symptoms.

Consider an alternative medicine with a better safety profile, for the management of insomnia during pregnancy.

Non-drug treatments should also be employed.

If zopiclone is the medicine of choice during pregnancy, use the lowest effective dose for the shortest duration possible. Inform neonatal care providers regarding maternal use of zopiclone 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 zopiclone in utero.

Breast feeding

Very small amounts of zopiclone are excreted into breast milk, but these amounts are unlikely to pose harmful effects to the breastfed infant.

In women who choose to breastfeed their healthy full-term infant while taking zopiclone, 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 zopiclone via breast milk.

Adverse Effects

1. Allergic reactions.

2. Sedation.

3. Hallucinations

4. As for the benzodiazepines in general, effects are potentiated with alcohol and other CNS depressant agents.

5. Sleep disorders:

   As with zolpidem, zopiclone 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. Addiction, tolerance and withdrawal symptoms:

   - As for the benzodiazepines; addiction, tolerance and withdrawal symptoms can all occur with zopiclone use.
   - Continuous long term use of zopiclone is **not** recommended and should not exceed **four weeks**.

Dosing

Usual adult dosing is:

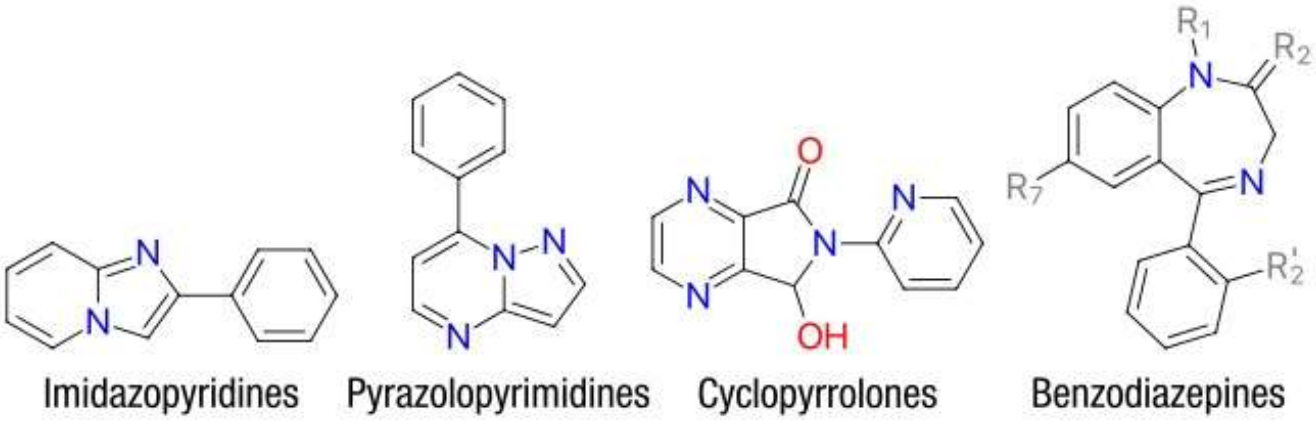
- 7.5 mg orally at night for up to 4 weeks.
- Reduce to 3.75 mg if possible.

For elderly, debilitated, significant respiratory, renal or hepatic impairment, initially 3.75 mg at night.

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 2018

2. Zopiclone in Australian Medicine's Handbook Website, Accessed June 2017.

3. Zopiclone in MIMs Website, 1 April 2016.

4. Zopiclone in RWH Pregnancy and Breastfeeding Guidelines, 19 July 2016.

Dr J. Hayes
Reviewed June 2018