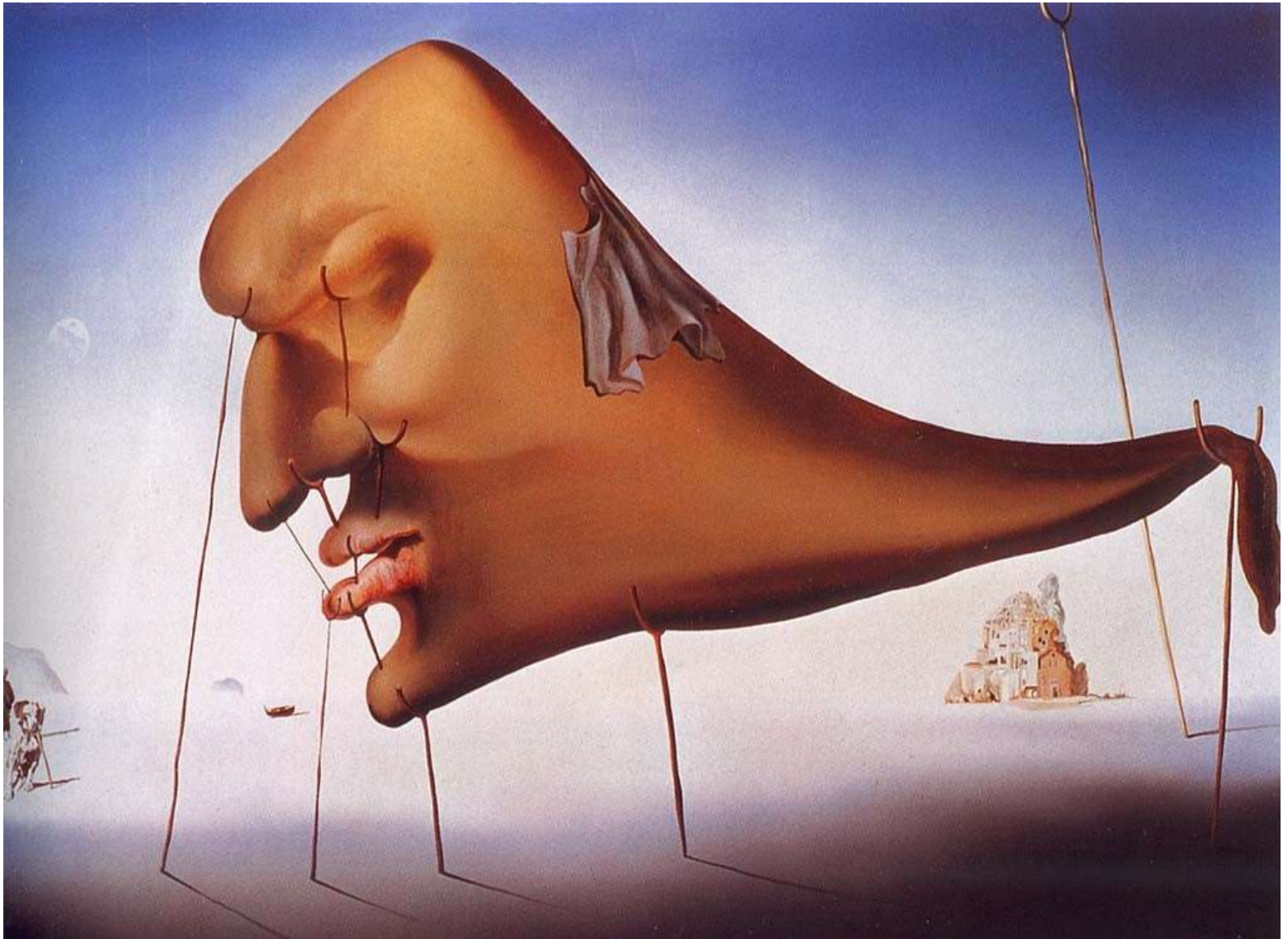


LORAZEPAM



"Sleep", oil on canvas, 1937, Salvador Dali.

"I have often imagined the monster of sleep as a heavy, giant head with a tapering body held up by the crutches of reality. When the crutches break we have the sensation of falling"

Salvador Dali, "The Secret Life of Salvador Dali", 1937.

I do all my work subconsciously. I never use models or paint from life or landscapes. It is all imagination. That is, I see everything in a dream as I am working, and when I have finished a picture, I decide what the title is to be. Sometimes it takes a little time before I can figure out what I have painted. The scenes in my imagination all have Spain in the

background - my own Catalonia or, perhaps the south of Andalusia....My ambition is to give the world of the imagination the same degree of objectivity and reality as the everyday world. What surrealism revolutionizes above all is art's themes, and to express these I use the same means as always. It's the themes, derived from Freudianism, that are new. In this way, using the most habitual and traditional means, the images are more effective and convincing. Abstraction has led to decorativism, while my method goes back to the great sources of painting. I now look at the pictures of Vermeer, Leonardo etc. And concentrate (as well as on their technique) on their enigma side, which we need to examine afresh, differently. In a word, we have to rewrite the history of painting....The subconscious has a symbolic language that is truly a universal language, for it does not depend on a special habitude or state of culture or intelligence, but speaks with the vocabulary of the great vital constants, sexual instinct, feeling of death, physical notion of the enigma of space - these vital constants are universally echoed in every human. To understand an aesthetic picture, training in appreciation is necessary, cultural and intellectual preparation. For Surrealism, the only requirement is a receptive and intuitive human being.

Salvador Dali

The Surrealists of the 1930s and 40s, and Salvador Dali in particular, were fascinated by Sigmund Freud and his theories on the subconscious mind. Freud believed that one of the keys to understanding the subconscious was through the analysis of dreams. When asleep, the mind is free of all distracting sensory input from the environment, leaving it free to roam its own inner world of subconscious thoughts, only vaguely perceived in the real world, or not perceived at all. By understanding the subconscious, it was claimed, a greater understanding of not only the individual person, but also of Homo sapiens in general, could be achieved. As Freud explored the subconscious through his techniques of "psychoanalysis", so Dali explored it through his Art. The dream was a constant and powerful motif that ran through Dali's works, and they struck a deep and universal chord in the mind of the greater public, a cord that crossed language and cultural barriers alike.

One of Dali's most famous works was "Sleep", of 1937. We see an enormous disembodied head, representing the mind in a vast barren surreal blue summer plane. As in a dream there is an awareness of self – or thought - but not of the physical body, which tails off into an insubstantial deflated balloon. The crutches of reality suspend the mind. At any time should a crutch fail – the mind will be instantly brought back to the real world. The ear is covered by a cloth and the eye is closed, symbolized the shutting out of sensory input from the real world. In the far distance a beached boat is seen, symbolizing severance from the normal environment. In the distance on the right is an image or mirage of what Dali described as "the well-known summering town from the boring dream of Piero della Francesca". A small dog on the left is also seen asleep in the hot summer sun. It too is also dreaming - supported by the crutches of reality.

Freud and Dali believed that as a species we need to reconnect with our subconscious mind in order to understand both ourselves and human nature in general more fully. In the frantic pace of modern living quality sleep can be a rare experience, and so from time to time medicinal agents such as lorazepam may help us to reconnect with our hidden levels of consciousness.

LORAZEPAM

Introduction

Lorazepam is a medium duration acting benzodiazepine.

Outside of Australia it is available as both oral and IV formulations, but in Australia only the oral preparation is available.

It is a medium duration benzodiazepine. It has a duration of action that is longer than midazolam, but shorter than diazepam.

In the ED setting it is a useful agent for mild anxiolysis/ sedation in patients for whom oral medication is appropriate.

See also separate Documents on:

- **Benzodiazepine overdose, (in Toxicology folder)**
- **Benzodiazepine withdrawal syndrome, (in Toxicology folder)**
- **Flumazenil, (in Drugs folder)**

History

The benzodiazepines were developed in the late 1950s.

Chlordiazepoxide was the first marketed as “Librium” in 1959

Diazepam was the second benzodiazepine developed and was marketed as “Valium” in 1963. It was described as a “minor tranquilliser” (as an alternative to the barbiturates).

Lorazepam was introduced to clinical practice by Wyeth Pharmaceuticals in 1977.

Preparation

Outside of Australia lorazepam is available as both oral and IV formulations, but in Australia only the oral preparation is available.

Tablets:

- **1 mg, 2.5 mg.**

Mechanism of Action

The exact mechanism of action of the benzodiazepines is incompletely understood, but most current theories hold that they potentiate the action of the endogenous CNS inhibitory neurotransmitter gamma-aminobutyric acid (or **GABA**)

There are GABA-A and GABA-B receptors.

Classification

Lorazepam is classified as a medium acting benzodiazepine (see **Appendix 1 below**).

Pharmacokinetics

Absorption:

- Lorazepam can be administered orally or IV

Distribution:

- Lorazepam is approximately 90% bound to plasma proteins.

Metabolism and excretion:

- Lorazepam is metabolized in the liver, mainly to the inactive glucuronide of lorazepam.

Pharmacodynamics

As with most other benzodiazepine agents, principle effects include:

1. Anxiolysis
2. Sedation
3. Hypnotic
4. Skeletal muscle relaxant
5. Antiepileptic effects.
6. Anterograde amnesia

Its duration of action is around **12- 24 hours**.

Indications

In the ED:

In the ED setting lorazepam is a useful agent for mild anxiolysis/ sedation in patients for whom oral medication is appropriate.

Its duration of action is around **12- 24 hours**.

Outside the ED:

1. Anxiolysis:
2. Sedation
3. Alcohol withdrawal symptoms.
4. Reduction of sympathetic hyperactivity
 - In particular in toxicology in cases of sympathomimetic hyperactivity.

Other indications include:

5. Muscle spasm - skeletal muscle relaxation.
6. As a premedication to anaesthesia
7. Hypnotic-sedative withdrawal syndromes.

Contraindications/ Precautions

Contraindications and Precautions to the benzodiazepines as a group include:

1. CNS depressant effects are synergistic with other CNS depressants including alcohol.
2. Chronic obstructive airways disease with incipient respiratory failure, particularly those who are CO₂ retainers.
3. Sleep apnea.
4. Contraindicated in myasthenia gravis.
5. Children and the elderly are more susceptible to the effects of benzodiazepines in general
6. Contraindicated in severe hepatic impairment, particularly when hepatic encephalopathy is present. In mild-to-moderate impairment, use lower doses of a short-acting benzodiazepine to reduce risk of precipitating coma.
7. There is increased sensitivity to CNS effects in patients with severe renal impairment; use lower doses in severe impairment.
8. Known hypersensitivity to benzodiazepines or any of the components of the formulation

9. Caution must be exercised in prescribing temazepam to individuals known to be **addiction prone**.

Pregnancy

Lorazepam is classified as a category C 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

Breastfeeding

Compatible; but caution with chronic use, monitor infant for drowsiness.

Adverse Effects

General adverse effects of the benzodiazepines as a group include:

1. Excessive respiratory depression:
 - This is usually seen in association with other factors that impair respiratory drive, (e.g. COPD, other CNS depressants, sleep apnea)
2. Excessive somnolence/ CNS depression:
 - Usually in the setting of excessive dosing or when used in association with other CNS depressants.
3. Physical dependence:
 - A benzodiazepine withdrawal syndrome is possible.
 - Patients who have been on longer term therapy of benzodiazepines should not have these *abruptly* withdrawn.
4. Psychological dependence:
 - Paradoxical hyper-excitement reactions are rarely seen, (mainly children or elderly).
5. Tolerance:
 - Tolerance, as defined by a need to increase the dose in order to achieve the same therapeutic effect, rarely occurs in patients receiving recommended doses under medical supervision.

- Tolerance may occur with longer term use, especially in those with drug seeking behaviour.
6. Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Dosing

In the ED:

Acute agitation/ anxiety in the ED:

- Give **1 - 2 mg** orally as a stat dose.

Outside of the ED: ²

Anxiety

- *Adult*, oral 2 - 3 mg daily in 1- 3 doses. Range 1- 4 mg.

Elderly and/or debilitated patient

- *Oral*, initially 1 - 2 mg daily in 1 or 2 doses, adjusted as needed.

Insomnia

- *Adult*, oral 1 - 2 mg at night.

Premedication

- *Adult*, oral 2 - 4 mg the night before and/or 1–2 hours before the procedure.

Reversal of effects:

Flumazenil is a specific benzodiazepine antagonist and will rapidly reverse the effects of benzodiazepines including depression of respiration and conscious state.

Appendix 1

Classification of Benzodiazepines:

Length of Action	Half-life	Drugs
Very short	< 6 Hours	Midazolam, Triazolam.
Short	6-12 Hours	Temazepam, Oxazepam, Alprazolam.
Medium	12-24 Hours	Lorazepam, Bromazepam.
Long	> 24 Hours	Diazepam, Nitrazepam, Flunitrazepam, Clobazam, Clonazepam.

References

1. eTG - November 2014.
2. Lorazepam in Australian Medicines Handbook Website, Accessed March 2016.
3. Lorazepam in MIMs Website April 2012.

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