

HALOPERIDOL



“The Courtyard in the Hospital at Arles”, oil on canvas, Arles, April 1889, Vincent van Gogh.

Vincent remembered little about his attacks (“I don’t know anything about what I said, what I wanted, or what I did”, he wrote), but he remembered the darkness. In an instant, “the veil of time and the fatality of circumstances seemed to be torn apart”, he said - as if he had suddenly and inexplicably disappeared from the world. A witness at the hospital who saw him during an attack described him as “lost”. In the darkness, nameless fears overwhelmed him. He felt waves of “anguish and terror” and “horrible fits of anxiety”. He lashed out violently at the threats he saw everywhere, raging incoherently at doctors and chasing away anyone who approached his bed. When his rage was spent, he retreated to a corner or under the covers and cowered in fevers

of “indescribable mental anguish”. He trusted no one, recognized no one, doubted everything he heard or saw, took no food, could not sleep, would not write, and refused to talk.

In the darkness, shapeless shadows pursued him. Horla-like ghosts – “unbearable hallucinations” - appeared and disappeared like vapour, but as vivid and palpable as his own flesh. “During the crises themselves”, he wrote, “I thought that everything I imagined was real”. They spoke to him. They accused him of terrible crimes. They called him “a deplorable and melancholy failure”, a “weak character”, a “miserable wretch”. He shouted back, desperately defending himself against the thin air. But he could not make himself heard. After a lifetime of arguing and persuading, he was trapped in his worst nightmare: a prisoner at the bar, gagged into silence. “I cried out so much during the attacks”, he recalled; “I wanted to defend myself and couldn’t do it”. The unanswered accusations sent him spiralling into seizures of self-loathing and “atrocious remorse”.

Vincent never identified his phantom accusers. But in his hours of “frightened suffering...when I was so far gone that it was more than a swoon”, he called out names; Degas, whose easy, elegant lines eluded him: Gauguin, whose refusal to stay in Arles confirmed the failure of his great Midi dream: Theo, who came to Arles too late, and for all the wrong reasons. And, of course, the daunting parson who relentlessly tallied every failure and spied from every crucifix.

“During my illness”, Vincent wrote, “I saw every room of the house at Zundert, every path, every plant in the garden, the views from the fields round about, the neighbours, the graveyard, the church, our kitchen garden behind - down to the magpie’s nest in a tall acacia in the graveyard”.

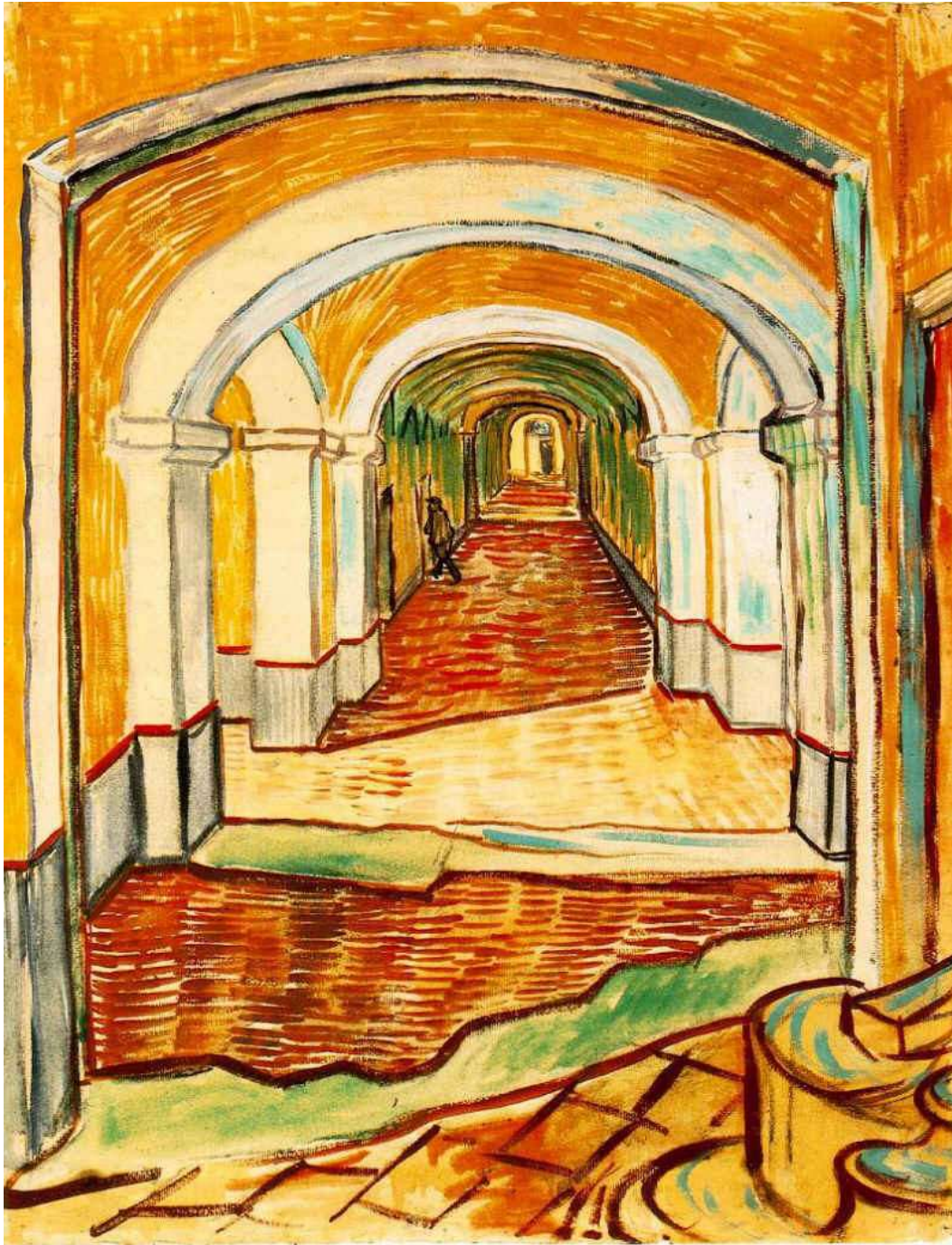
In such hallucinatory “eruptions of memory”, as Flaubert called them, Vincent revisited all the injuries of the past. “In my madness”, he recalled, “my thoughts sailed over many seas”. For him, memory had always been the imagination’s sixth sense: nostalgia, a turbulent inland sea of inspiration. His delirium breached the dam between past and present. Flaubert, who suffered similar mental seizures, described how images flooded in, “like torrents of blood...everything in one’s head bursting all at once”.

Where others saw madness, Vincent saw memories. He climbed into bed with fellow patients, just as he had done with Theo in Zundert. He chased after nurses in his nightshirt, just as he had done with Sien in The Hague. He even blackened his face with coal, just as he had done in the Borinage. To Rey it looked like an act of lunacy – “he went to wash himself in the coal bin”, the doctor reported incredulously. What Rey couldn’t see, what only Vincent could see, was a past of ridicule and rejection by the wretched Borins and a familiar self-abasing ritual of solidarity with the miners who, like him, “walked in darkness”. Sometimes the darkness passed quickly - a sudden storm that blotted out the Sun for a moment or an hour. Other times, it lingered for days as storm after storm battered his reason and seemed to banish the Sun forever.

By December 30, the darkness had lifted. Or so it seemed. “His condition has improved”, Rey wrote to Theo that day, exactly a week after Vincent took up his razor. “I don’t believe his life is in danger, at least for the moment”. When he emerged, Vincent found himself imprisoned and alone. “Why do they keep me here like a convict?” he angrily demanded. Stripped of recollection, he felt only guilt. “He hides himself in absolute silence”, one visitor reported. “covers himself with his bedclothes and at times cries, without uttering a single word”.

Steven Naifeh and Gregory White Smith, Van Gogh, the Life; 2011.

Pulitzer prize winners Steven Naifeh and Gregory White Smith in their description of Vincent van Gogh's mental illness at Arles, powerfully and poignantly describe the horrific torments of the severely psychotic in an age before effective antipsychotic drugs were available. Vincent's nightmarish apparitions could have been effectively controlled with Twentieth century drugs such as haloperidol, though these would not be discovered until over half a century after his death. Out of his tragic illness, however came his way of coping – he gave the world post-impressionist Art, the forerunner of many genres that would evolve during the course of the Twentieth century and by so doing he would evolve, diversify and enrich Art and all our lives, forever.



*"Corridor in the Asylum of Saint-Paul", black chalk and Gouache, Saint-Remy, October 1889.
Vincent van Gogh.*

HALOPERIDOL

Introduction

Haloperidol is a first-generation antipsychotic agent.

It was extensively used in the past as a first line anti-psychotic agent, having largely replaced the older first generation antipsychotic agent, chlorpromazine.

Haloperidol is still currently used, but within the first-generation antipsychotic drug group, droperidol is now generally preferred because of its greater sedating effect.

See also separate documents on:

- **Antipsychotic overdose (in Toxicology Folder)**
- **Benztropine (in Drugs Folder)**

Preparations

Ampoules:

- **5 mg/1 mL / 10 mg/1 mL / 20 mg/2 mL**

Tablets:

- **0.5 mg/ 1.5mg/ 5.0 mg**

Oral liquid:

- **2 mg/mL in 100 ml bottle.**

Haloperidol decanoate

- **This is a long acting (about one month) IM depot form of haloperidol**

Chemistry

Haloperidol is a neuroleptic drug of the butyrophenone group that also includes Droperidol

Mechanism of Action

Antipsychotic actions are thought to be mediated (at least in part) by blockade of dopaminergic transmission in various parts of the brain (in particular the limbic system).⁴

Evidence suggests:

- **All effective antipsychotics block D2 receptors**

- Differential blockade of other dopamine receptors (eg D1) may influence therapeutic and adverse effects
- Antagonism of other receptors may influence antipsychotic activity, e.g. 5HT₂ antagonism with some agents.

Pharmacodynamics

1. CNS:
 - Sedative:
 - ♥ Haloperidol is not as sedating as droperidol.
 - Antipsychotic
2. Antiemetic
3. Respiratory
 - There is no significant respiratory depression
4. Myocardial effects
 - There are no significant myocardial depressant effects

Pharmacokinetics

Absorption:

- Haloperidol can be given IV, IM or orally.

Orally:

Haloperidol is rapidly absorbed from the gastrointestinal tract following oral administration but appears to undergo first-pass metabolism in the liver.

Peak plasma levels of haloperidol occur within two to six hours of oral dosing

IM:

Peak plasma levels of haloperidol occur about **20 minutes** after **IM** administration.

Distribution:

- Haloperidol is approximately 92% bound to plasma proteins.
- Haloperidol is distributed into breast milk.

- Haloperidol is highly lipid soluble and may remain in fatty tissue for some weeks.

Metabolism and excretion:

- Haloperidol is metabolised in the liver.
- The CYP3A4 and/or CYP2D6 enzymes are involved in the metabolic biotransformation of haloperidol.
- The mean plasma half-life (terminal elimination) after oral dosing is around 21 hours.

Indications

Current indications include:

- Acute and chronic psychoses:

Acute agitation associated with an acute psychotic episode (such as schizophrenia or drug induced psychosis) or mania:

Note however that droperidol is generally now preferred over the more traditional **haloperidol** for acute behavioural emergencies because it is **more sedating**, has a **quicker onset of action**, a **shorter half-life** and is **less cardiotoxic** than haloperidol.

- Acute mania
- Tourette syndrome and other choreas
- Adjunct in treatment of hallucinations due to alcohol withdrawal (if diazepam is inadequate).

Contraindications & Precautions

These include:

1. Patients with reduced conscious state, (unless the airway is protected).
2. Hypotensive patients
3. Known hypersensitivity to haloperidol
4. Parkinson's disease:
 - Risk of aggravation
5. Caution in patients with epilepsy - may lower seizure threshold.

Pregnancy

Haloperidol is classed as a **group C** drug in pregnancy.

Group C drugs are those 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.

Breast feeding

Caution, insufficient data

Adverse Effects

Haloperidol shares many of the adverse **acute** and **chronic** effects of the first generation anti-psychotic major tranquillizing drugs.

Adverse effects include:

1. CVS effects:
 - Hypotension:
 - ♥ Alpha-receptor blockade results in vasodilation.
 - ♥ Orthostatic hypotension can occur in ambulant patients
 - ♥ Synergistic action with other drugs that can cause hypotension.
 - QT prolongation:
 - ♥ This is uncommon, but probably more common than that seen with droperidol.
 - ♥ Cardiotoxicity is more likely to occur when given **IV in excessive doses**.
2. Respiratory:
 - Some respiratory depression
 - Synergistic with other CNS depressants.
3. CNS:
 - Excessive sedation:
 - ♥ Including synergistic effects with other CNS depressants.

- Seizures:
 - ♥ May lower convulsive threshold in the pre-disposed
- Hypothalamic effects:
 - ♥ Impaired thermoregulation
 - ♥ Weight gain
- Extrapyrarnidal effects:

As with any major tranquillizing agent these can include:

- ♥ Dystonic reactions
- ♥ Tardive dyskinesia, (with chronic use):

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the **duration** of treatment and the **total cumulative dose** of the drug increases. Less commonly, the syndrome can develop after relatively brief treatment periods at low doses. The risk seems to be greater in elderly patients. ⁴

- ♥ Akathisia:

A feeling of motor restlessness; usually occurs 2- 3 days (up to several weeks) after starting treatment and may subside spontaneously. It is important to differentiate between akathisia and agitation secondary to psychosis. Akathisia tends to improve with dose reduction and deteriorate when the dose is increased; agitation due to psychosis tends to improve if the dose is increased and deteriorate if it is reduced. ²

- ♥ Parkinson's type syndromes:

Includes tremor, rigidity or bradykinesia; usually develops after weeks or months. Although usually reversible, symptomatic treatment is sometimes necessary. Short-term use of an anticholinergic (benztropine or benzhexol) may help.

4. Neuroleptic malignant syndrome.

5. Anticholinergic effects:

Haloperidol has only mild anticholinergic effects, which may include:

- Tachycardia/ dry mouth/ blurred vision/ aggravation of narrow angle glaucoma/ urinary retention/ reduced GIT motility - constipation.

Dosing

IM/ IV:

IM dosing is preferred to IV dosing,(to reduce the risk of cardiovascular toxicity).

Haloperidol IM dose: 5 to 10 mg IM, (or IV with caution) up to 20 mg in 24 hours. ¹

Half these doses should be used in the **frail elderly** patient as a general rule.

Higher doses may be used in some circumstances, but with caution and close monitoring.

Oral:

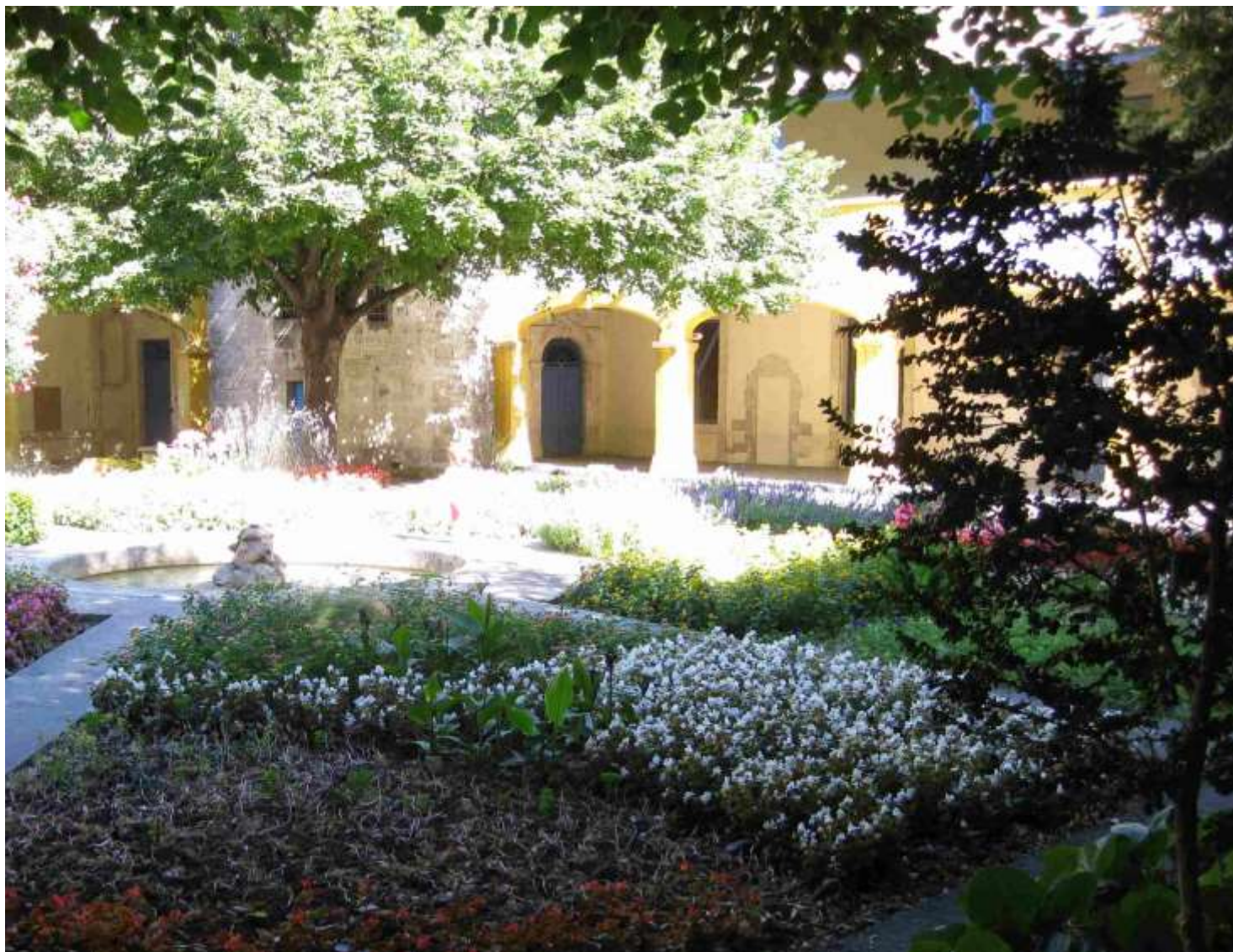
Generally dosing ranges from **0.5 mg - 15 mg** daily, taken at night.

Higher doses may be used in some circumstances, but with caution and close monitoring.

Depot Injection:

Long-acting IM depot: 50 - 300 mg every 4 weeks.

100 mg corresponds roughly to a daily dose of 5 mg orally.



The Courtyard in the Hospital at Arles 2012, (photograph, by Dr Andrew Casamento).

References

- 1 eTG- July 2014.
2. Haloperidol Australian Medicines Handbook, July 2013
3. Haloperidol in MIMs, Accessed August 2014.

Dr J. Hayes.
1 August 2014