

FLUVOXAMINE



"The Garden of Earthly Delights", (detail) c. 1504, Right panel: Triptych plus shutters, oil on panel, Hieronymus Bosch, Museo del Prado, Madrid.

*...Nessus had not yet reached the other side
when we made our way into a forest
not marked by any path.*

*No green leaves, but those of dusky hue -
not a straight branch, but knotted and
contorted -
no fruit of any kind, but poisonous thorns.*

*No rougher, denser thickets make a refuge
for the wild beasts that hate tilled lands
between the Cecina and Corneto*

*Here the fifthly Harpies nest,
who drove the Trojans from Strophades
with doleful prophecies of woe to come.*

*They have broad wings, human necks and
faces,
taloned feet, and feathers on their bulging
bellies.
Their wailing fills the eerie trees.*

*And my good master then began to speak;
“Before you go deeper you should know,
you are, and will be, in the second ring*

*“until you reach the dreadful sand. Look
well -
you will see things that, in my telling,
would seem to strip my words of truth”.*

*Lamentations I heard on every side
but I saw no one who might be crying out
so that, confused, I stopped.*

*I think he thought that I thought
all these voices in among the branches
came from people hiding there.*

*And so the master said; “If you break off
a twig among these brambles
your present thoughts will be cut short”.*

*Then I stretched out my hand
And plucked a twig from a tall thorn bush,*

*and its stem cried out: “Why do you break
me?”*

*When it ran dark with blood
it cried again; “Why do you tear me?
Have you no pity in you?”*

*“We once were men that now are turned to
thorns.*

*Your hand might well have been more
merciful
had we been souls of snakes”.*

*As from a green log, burning at one end,
that blisters and hisses at the other
with the rush of sap and air,*

*so from the broken splinter oozed
blood and words together, and I let drop
the twig and stood like one afraid.....*

*The poet waited then he said to me:
“Since he is silent now do not waste time
but speak if you would ask him more”.*

*And I replied: “Please question him
about the things you think I need to know.
For I cannot, such pity fills my heart”.*

*This he began again: “So that this man may,
with ready will, do as your words entreat,
may it please you, imprisoned spirit,*

*to tell us further how the souls are bound
inside such gnarled wood, and tell us, if you
can,
if from such limbs one ever is set free:”*

*Then the tree forced out harsh breath, and
soon
that wind was turned into a voice
“My answer shall be brief.*

*“When the ferocious soul deserts the body
after it has wrenched up its own roots,
Minos condemns it to the seventh circle.*

*"It falls into the forest, in a spot not chosen,
but flung by fortune, helter-skelter,
it fastens like a seed.*

*"It spread into a shoot, then a wild thicket.
The Harpies feeding on its leaves,
give pain and to that pain a mouth...*

*When the master stopped beside it, he said,
"Who were you, that through so many
wounds
pour out with blood your doleful words?"*

*And he to us, "Oh souls who have arrived
to see the shameless carnage
that has torn me from my leaves,*

*"gather them here at the foot of this
wretched bush.
I was of the city that traded patrons -*

*Mars for John the Baptist. On that account
"Mars with his craft will make her grieve
forever.*

*And were it not that at the crossing of the
Arno some vestige of him still remains,*

*"those citizens who afterwards rebuilt it
upon the ashes that Attila left behind
would have done their work in vain
I made my house into my gallows....*

*Urged by the love I bore my place of birth
I gathered up the scattered leaves and gave
them back
To him, who had by this time spent his
breath.*

*Dante Alighieri,
The Inferno, Bk XIII (1306-1317)*

Dante and Virgil have now reached the horrific Seventh Circle of Hell, wherein are cast the damned souls of the suicides. The monstrous long tailed beast, Minos, is the judge of Hell. He casts the suicides into the Seventh Circle. The shade of the damned is thrown into the soil becoming incorporated into it, "helter-skelter, like a seed". From this seed a dense bush grows, its leaves taken as food by the terrifying Harpies who nest in them, leaving behind only poisoned thorns. Each leaf a Harpy takes from the bush, causes the shade terrible pain. Virgil tells Dante to break off one of the thorns, then he will understand the true horror of what happens in this place. When Dante breaks off a thorn it bleeds and shrieks out in pain, "Why do you tear me? Have you no pity in you?" Dante is aghast, unable to bring himself to talk to the imprisoned spirit. He asks Virgil to speak for him; "Please question him about the things you think I need to know. For I cannot, such pity fills my heart".

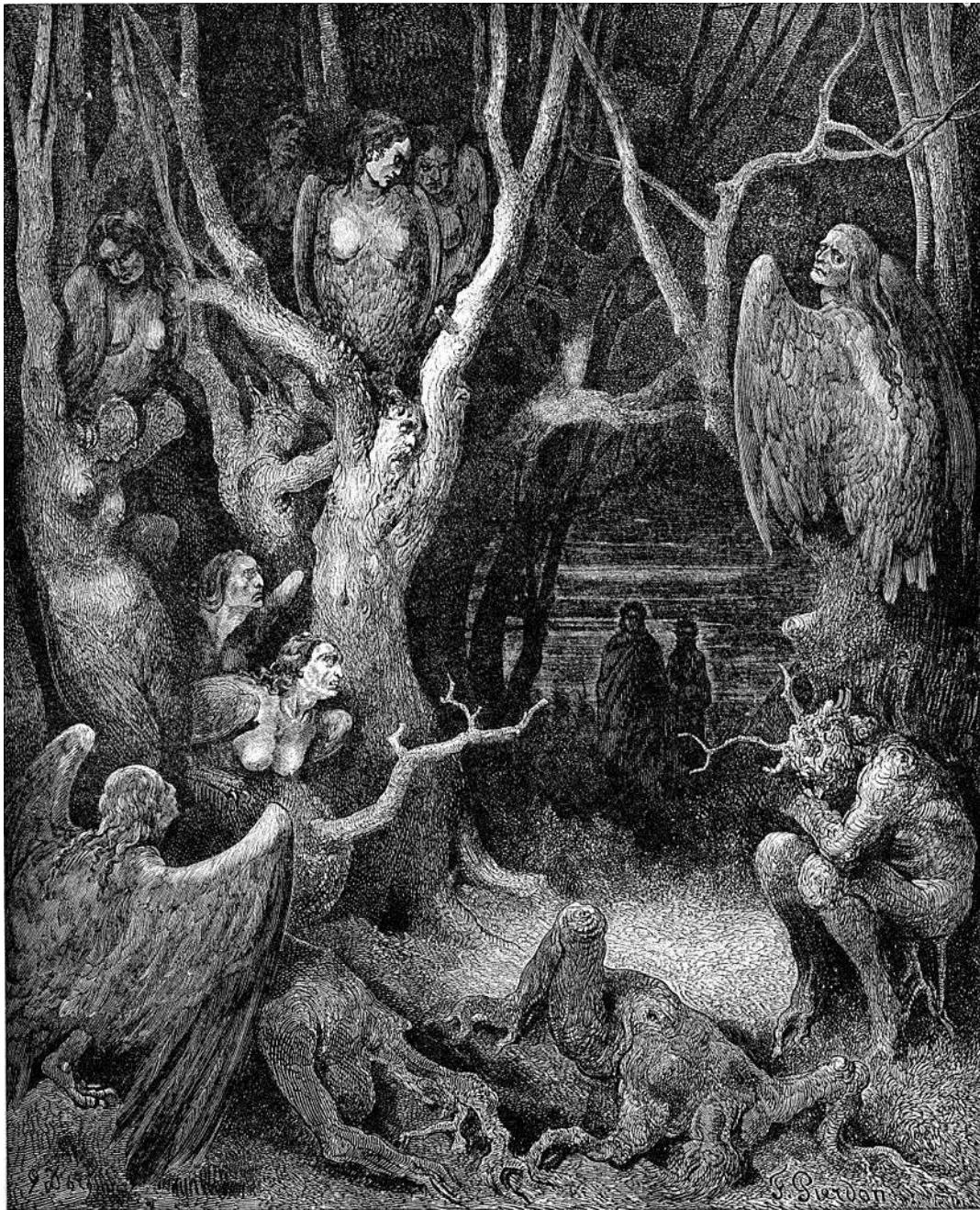
"I was of the city that traded patrons" the voice replies, "Mars for John the Baptist". It is clear from this, that in life the shade was a Florentine. The city was originally founded by Rome, and as a military base it took the god of war, Mars, as its protector. But in the Christian era Florentines replaced the pagan deity with St. John the Baptist as the city's guardian and defender. The only remaining vestige of Florence's pagan past, is an ancient Roman statue of Mars at the foot of a bridge that crosses the Arno; "at the crossing of the Arno some vestige of him still remains..." Dante then finally understands that the shade has been commended to the eternal torments of the Seventh Circle for the "sin" of suicide; "I made my house into my gallows...." Dante is filled with so much pity, for his fellow Florentine, he tries some desperate way to alleviate his suffering; "Urged by the love I bore my place of birth, I gathered up the scattered leaves and gave them back, to him...."

Medieval Christianity saw suicide as a mortal sin, even though there is no specific mention of suicide in the New Testament. This harsh theology appears to have been originally based on the works of St. Augustine, who in the Fifth Century A.D wrote his famous book, "The City of God", which would have such a profound influence on Christian thinking. In it he makes the overall case for Christianity's first condemnation of suicide. His justification for this was based on his interpretation of the fifth commandment, which simply states, "though shalt not kill". He took this to mean that this included the killing of one self. Life was a gift from God, and to take it is a sin against God, be it the life of "thy neighbour" or of one self. So strong did this belief become within medieval Christian theology, that those who committed suicide could not be buried in hallowed (or Church) grounds. In extreme cases bodies were mutilated, and the families of suicides were victimized.

*In the Medieval mind, therefore, the souls of suicides would be condemned to Hell. The horrific apogee of medieval imagery of this state of being is expressed in the literary arts, in Dante's *Inferno* of the *Divine Comedy* and in the visual arts in the right panel of Hieronymus Bosch's, triptych, "The Garden of Earthly Delights". The enigmatic "Tree Man" is the dominating feature of Bosch's vision of Hell. It is a disturbing image that does well in conjuring up Dante's shade of the suicide in the forest of the Harpies in the Seventh Circle of Hell. The magisterial Art commentator Larry Silver has described the unsettling recurring motif of figures that stare out directly back at the viewer as if pleading for help. No better example is provided by the tree-man. His body has been morphed into the leafless, thorn ridden tree of Dante's damned Florentine. Its visage is pale lifeless and stone gray, there is no greenery, it is an image of death. His feet are balanced precariously on barges that float in black pitch or equally could be barren earth. His right leg is bandaged. There is a hint of blood dripping beneath it. Perhaps it is the wound left behind when Dante broke off a thorn. His body is hollowed out into a dark tavern inhabited by demons that seem to be engaged in mysterious and sinister activities. A ladder reaches up to the tavern, at the bottom of which is a winged demon ushering naked figures up it, who have been shot by arrows in unspeakable places. Atop his head is a round platform upon which other naked shades are paraded around by demons in endless circles to the mocking accompaniment of music from a giant hybrid lute and bagpipes. It is an image that mirrors well Dante's eternal Circles of Hellish torment.*

The theology of suicide as a mortal sin has had a very long and miserable history. Beginning with St. Augustine in the Fifth century A.D, it lasted until very recently when Pope Pius X decreed "In the Fifth Commandment God forbids suicide, because man is not the master of his own life no more than of the life of another. Hence the Church punishes suicide by deprivation of Christian burial". This is not the view of more enlightened modern day Pontiffs, such as Pope Francis I. In our more enlightened age suicide is no longer viewed as a "mortal sin", rather a terrible illness of the mind. By our medical science we strive to understand the biological reasons for severe depression, whose natural history not uncommonly ends in the tragedy of suicide. Popular Twentieth century medical thinking attributed depression to the simplistic theory of "chemical imbalances" within the brain. Big Pharma were only too happy to agree. They had after all struck gold with this philosophy. Today the pharmaceutical industry dominates the treatment of major depression; however the human psyche is a most complex entity. The simple elevation of central nervous system neurotransmitters gives "variable" results... at best. We still have much to understand about it if we are even to even hope to be able

to treat depression effectively. This understanding will come not only via pure science by also by the humanities. From Mathematician and Astrophysicist to Writer, Musician and Artist, each human mind is a product of both to variable degrees; it is never all one or all the other. Both Dante and Bosch were products of their times, and so their understanding was constrained when it came to the sciences. Where both excelled however, perhaps among the most brilliant minds of our species was in the humanities and in these their genius, unlike much of our shifting-sand understanding of science, was ageless.



"Dante and Virgil in the Forest of the Suicides", 19th century, woodcut print, Gustave Dore

FLUVOXAMINE

Introduction

Fluvoxamine (brand name in Australia “**Luvox**” among others) is a selective serotonin reuptake inhibitor (**SSRI**) antidepressant.

It is as effective as the first generation agents for the treatment of depression and although not nearly as lethal in overdose as those agents, nonetheless is not without its own significant side effects.

See also separate documents on:

- **SSRI Overdose (in Toxicology folder)**
- **Serotonin Syndrome (in Toxicology folder)**

History

The SSRIs were developed in order to have safer less toxic antidepressant agents, than the tricyclic antidepressants or MAOIs that were the front line antidepressants of the 1970s and early 1980s.

Fluoxetine was developed by Klaus Schmiegell and Bryan Molloy of the Eli Lilly Company in 1972 and was introduced into medical practice as “Prozac” in 1986. It was the prototype SSRI and quickly became the one of the greatest selling drugs of all time, peaking at a staggering 2.6 billion USD a year.

Fluvoxamine was introduced into clinical practice in the US in 1994.

Chemistry

Fluvoxamine is a member of a class of antidepressant agents known as selective serotonin reuptake inhibitors (SSRIs).

It is chemically unrelated to the tricyclic antidepressants, and to other serotonin reuptake inhibitors as it is a monocyclic compound.

Fluvoxamine has two isomeric forms: an E isomer which is pharmacologically active, and a Z isomer which is non-active.

Classification

Antidepressants can be loosely classified into 6 groups:

1. **Tricyclic antidepressants (TCAs):**

TCAs inhibit the reuptake of **noradrenaline** and **serotonin** into presynaptic terminals.

Examples include:

- Amitriptyline
- Dothiepin
- Doxepin
- Imipramine
- Nortriptyline
- Trimipramine

2. **Monoamine oxidase inhibitors (MAOIs):**

These agents block of MAO-A and/ or MAO-B, thereby increasing the synaptic concentrations of **adrenaline, noradrenaline, dopamine** and **serotonin**.

Examples include:

- Phenelzine
- Tranylcypromine

3. **Selective serotonin reuptake inhibitors (SSRIs):**

The SSRIs selectively inhibit the presynaptic reuptake of **serotonin**

Examples include:

- Citalopram
- Dapoxetine
- Escitalopram
- Fluoxetine
- **Fluvoxamine**
- Paroxetine

- Sertraline

4. **Serotonin- norepinephrine reuptake inhibitors (SNRIs):**

These are **serotonin** *and* **noradrenaline** reuptake inhibitor.

Examples include:

- Venlafaxine
- Desvenlafaxine
- Duloxetine

5. **Tetracyclic antidepressants:**

These have a tetracyclic chemical structure, containing four rings of atoms.

They are closely related to the tricyclic antidepressants (TCAs), which contain three rings of atoms.

Examples include:

- Mianserin
- Mirtazapine

6. **Atypical Antidepressants:**

Essentially other newer agents not belonging to the above groups

Broadly described as atypical antidepressants, they affect serotonin, norepinephrine, and dopamine levels in varied and unique ways.

Preparations

Fluvoxamine maleate as:

Tablets:

- 50 mg
- 100 mg

Mechanism of Action

The SSRIs selectively inhibit the presynaptic reuptake of serotonin (5- hydroxytryptamine, 5HT).

They do *not* block the reuptake of noradrenaline.

Pharmacodynamics

Fluvoxamine has an efficacy at least equal to that of tricyclic antidepressants and superior to placebo in the treatment of patients who have anxiety and/ or depressive symptoms.

Antagonism of muscarinic, histaminergic and α_1 -adrenergic receptors have been hypothesised to be associated with various anticholinergic, sedative and cardiovascular effects of classic tricyclic antidepressant drugs. Fluvoxamine binds to these and other membrane receptors from brain tissue **much less** potently *in vitro* than do the tricyclic drugs and so these adverse effects are not expected with the SSRI agents.

Pharmacokinetics

Absorption:

- Fluvoxamine is almost completely absorbed following oral administration.
The absolute bioavailability is 53%
- Maximum plasma levels occur within 3-8 hours of dosing

Distribution

- The Vd is estimated to be 20 L/kg.
- Human plasma protein binding is around 80 %
- Fluvoxamine can cross the human placenta.
- Fluvoxamine is excreted into human breast milk in small amounts.

Metabolism and excretion:

- Fluvoxamine undergoes extensive hepatic transformation, mainly via oxidative demethylation, into at least 9 metabolites, none of which are thought to be pharmacologically active.
- < 4% of the dose is excreted unchanged in the urine.

- The mean plasma half-life is approximately 12 - 13 hours after a single dose and approximately 22 hours following repeated dosing

Indications

Indications for fluvoxamine include

1. Major depression
2. Anxiety disorders:
 - Panic disorder
 - PTSD
3. Bulimia nervosa
4. Premenstrual dysphoric disorder
5. Obsessive-compulsive disorder

Contra-indications/precautions

These include

1. Known hypersensitivity to fluvoxamine or to other SSRIs
2. Caution with other **serotonergic** agents:
 - Coadministration with other serotonergic drugs (e.g. SNRIs, SSRIs, tramadol or triptans such as Sumatriptan, or MAOIs - selective, reversible or irreversible - within a minimum of 14 days) may result in **serotonin syndrome**.
3. Bipolar disorder: ²
 - All antidepressants may provoke a manic episode when used in people with **bipolar disorder**.

Some patients *without* a history of bipolar disorder may develop an antidepressant-induced manic episode; this does not necessarily imply a diagnosis of bipolar affective disorder.
4. Dose should be decreased in hepatic impairment:
5. QT prolongation:

- As for a number of other SSRIs, fluvoxamine should be used with caution in patients with conditions such as congenital long QT syndrome or acquired long QT syndrome (e.g. concomitant use with drugs that prolong the QT interval).

6. Children < 18 years:

- **Increased** suicidal thoughts and behaviour can occur **soon after** starting any antidepressant, particularly in young people; monitor patients frequently and carefully **early** in treatment.

This is particularly the case with the SSRIs. SSRI use in fact is related to a **higher** overall risk of suicidal behavior in children and adolescents and so SSRIs are **contraindicated** in these age groups.

7. Bleeding risk: ¹

- Selective serotonin reuptake inhibitors (SSRIs) may increase the risk of bleeding, especially gastrointestinal bleeding, by blocking the uptake of serotonin into platelets.

However, the absolute risk of this is **low**.

The risk is increased by concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulant drugs and antiplatelet drugs.

Patients with liver cirrhosis or liver failure and patients susceptible to gastrointestinal bleeding (e.g. patients with a history of peptic ulcer disease or oesophageal varices, or who are undergoing surgery) are also at increased risk.

Consider an alternative class of antidepressant or the addition of a gastroprotective drug (e.g. a proton pump inhibitor) in patients at increased risk of bleeding.

If NSAID use must be continued, a less gastrototoxic NSAID is recommended (e.g. ibuprofen, diclofenac).

Pregnancy

Fluvoxamine is a category class 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.

Most studies have shown there is no significant increased risk of congenital malformations following maternal use of selective serotonin reuptake inhibitors (SSRI) in early pregnancy.

Pregnancy complications such as preterm birth, spontaneous miscarriage and low birth weight following selective serotonin reuptake inhibitors (SSRI) in utero exposure have been reported, however the data are inconsistent and likely confounded by indication and other factors.

Neonatal withdrawal symptoms may develop due to prenatal exposure to fluvoxamine, especially in late pregnancy. These symptoms may include respiratory distress, irritability, temperature instability, sleep disturbance, tremors, jitteriness, feeding difficulties and diarrhoea, which can be attributed to serotonergic hyperstimulation.

The evidence concerning the association between persistent pulmonary hypertension of the newborn (PPHN) is still insufficient to contraindicate the use of SSRI in pregnancy. Inform neonatal care providers about the maternal use of fluvoxamine as supportive care may be required.

Studies regarding the long term behavioural and cognitive outcomes following infants exposed to SSRI in utero are limited. Most studies have shown no significant differences on neuro-behavioural development between the exposed and non-exposed children .

The association between maternal use of antidepressants and the risk of autism spectrum disorder and attention deficit/hyperactivity disorder in children are still controversial. Several studies suggest that prenatal use of SSRI may increase the risk of autism spectrum disorders and attention deficit/hyperactivity disorder in children. However, other studies disputed the findings. Published studies on prenatal SSRI exposure and autism spectrum and attention deficit/hyperactivity disorder should be cautiously interpreted due the possible presence of confounding factors such as maternal depression and genetic conditions in children. Further studies are needed to replicate and extend these findings.

Breast feeding

Small amounts of fluvoxamine are excreted into breast milk, but no serious harmful effects have been found in breastfed infants.

However, a case report of a 5-month-old infant developed severe diarrhoea, mild vomiting, agitation and decreased sleep within 2 days after maternal treatment of low dose fluvoxamine 50 mg daily.

If fluvoxamine is the medicine of choice, use the lowest effective daily dose and observe the breastfed infant for potential adverse effects such as excessive drowsiness, irritability, poor feeding and restlessness. Inform neonatal care providers immediately if any adverse effects are noted in the breastfed infant.

There is still a lack of information regarding the long term effects on developmental outcomes of infants exposed to fluvoxamine via breast milk.

Adverse Effects

These include the adverse effects of the SSRIs in general:

1. Allergic / hypersensitivity reactions.
2. GIT upset:
 - Nausea, diarrhoea
3. CNS effects:
 - Drowsiness/ mild sedation.
 - Serotonergic effects which occur in children > adolescents > adults.

These may include:

- ♥ Anxiety / agitation
- ♥ Panic attacks
- ♥ Insomnia
- ♥ Tremor

4. **Serotonin toxicity :**
 - A more serious serotonin toxicity can develop, particularly when used in combination with other serotonergic agents.

Treatment with either moclobemide or a MAOI (or within 14 days of stopping a MAOI or within 2 days of stopping moclobemide) is contraindicated due to the risk of serotonin toxicity.²

5. Sexual dysfunction
6. Hyponatraemia:
 - This usually occurs early in treatment, and may be asymptomatic. It is due to SIADH.
7. Prolonged QT interval:

- Occasionally, sertraline may prolong the QT interval and increase the risk of arrhythmia. Avoid use if other risk factors (including other drugs that affect the QT interval) cannot be avoided.

8. Children < 18 years

- Suicidal ideation may paradoxically be increased

Dosing

Start with lower doses and increase gradually as required.

When stopping any SSRI treatment it is advisable to taper over several weeks to avoid withdrawal effects; reduce the daily dose by half no faster than weekly.

Usual **adult** dosing is:

- Oral, initially 50 mg once daily.

Gradually increasing as necessary to 100 - 300 mg daily.

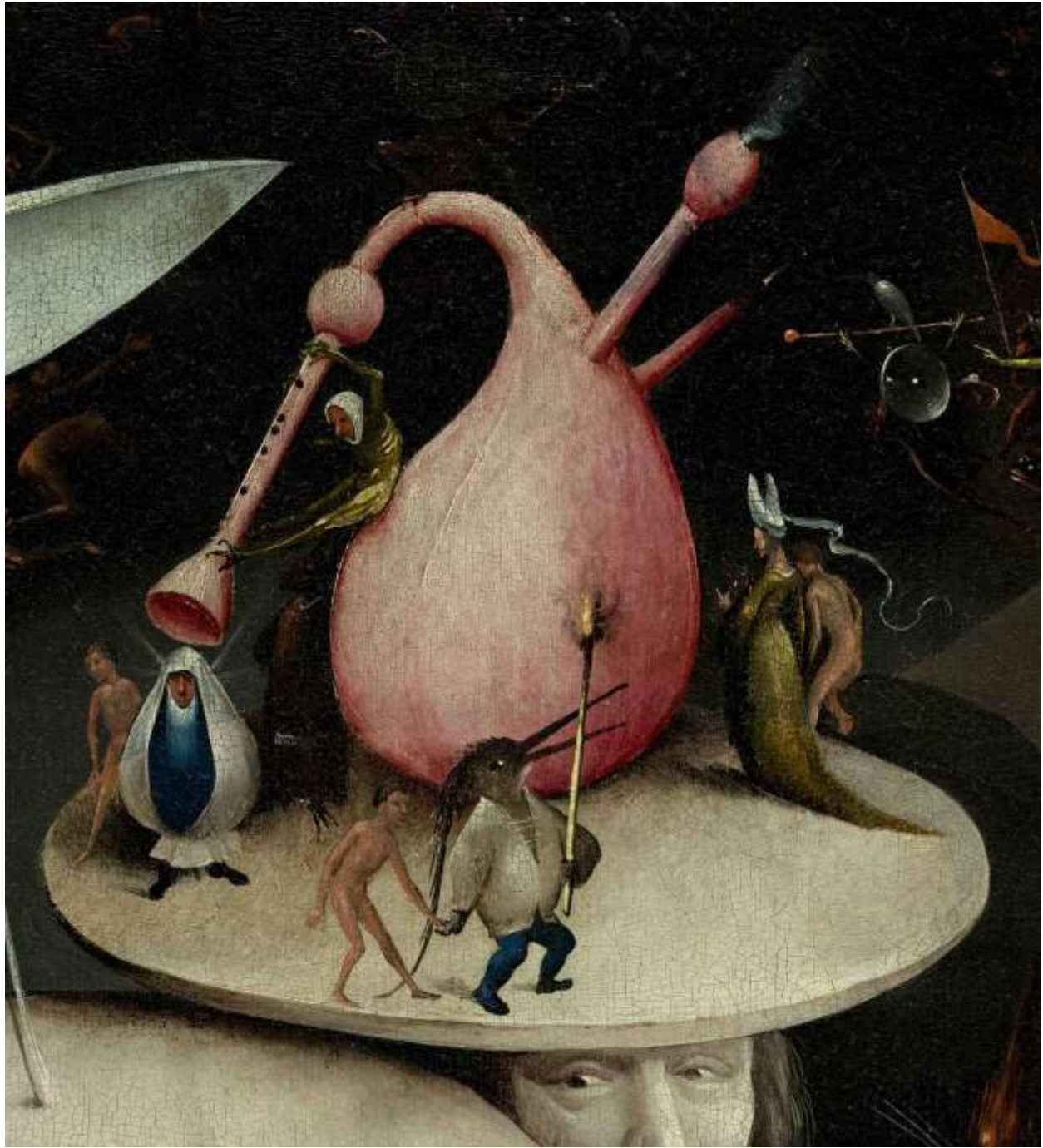
In **depression**, doses > 100 mg daily are not usually needed.

Give doses >150 mg in 2 or 3 doses.

Maximum daily dose should be 300 mg.

Hepatic impairment:

- Use a lower initial dose and titrate dose slowly.



"The Garden of Earthly Delights", (detail) c. 1504, Right panel: Triptych plus shutters, oil on panel, Hieronymus Bosch, Museo del Prado, Madrid.

References

1. eTG - July 2019.
2. Fluvoxamine in Australian Medicines Handbook Website Accessed, July 2019.
3. Fluvoxamine in MIMs Website, 1 July 2017
4. Fluvoxamine in RWH Pregnancy & Breastfeeding Guidelines; 10 April 2019.

Dr J. Hayes
July 2019