

PAROXETINE



Study for "Self Portrait Showing the Scar", pencil on paper, 1938, Frida Kahlo.

Frida's wounded self-portraits were a form of silent crying.

In images of her footless, headless, cracked open, bleeding, she turned pain into the most dramatic image possible in order to impress on others the intensity of her suffering. And by projecting pain outward and onto the canvas, she also extracted it from her own body. Self-portraits were fixed, immutable replicas of her mirror image, and neither reflections nor canvases feel pain.

As antidotes to pain, the wounded self-portraits may have served in another way. One thinks of the experience of catching a glimpse of one's reflection in a mirror at a moment of physical or emotional anguish. The image in the mirror is astonishing - it looks like us, but it does not share our pain. The disjunction between our sense of ourselves in pain (perceived from the inside out) and the surface evidence, offered by the mirror, of an apparently pain free self (seen from the outside in) can function as a steadying influence. The reflected image recalls to us our familiar physical self, providing a feeling of continuity. If Frida was drawn to mirrors because they comforted her in this way, painting the image she saw in the mirror was a way of making that reassuring image permanent. Thus self-portraits could serve as aids to objectivity or dissociation. Also, by looking at her wounded self in her paintings, Frida could sustain the illusion of being the strong, objective onlooker to her own misfortune....

Frida's powerful sexual appetite, both homo and heterosexual expressed itself in an unmistakable aura that fairly radiates from the surfaces of all her paintings. It permeates the more visceral of her still lifes, and is the principal subject of works like the 1944 panel, "Flower of Life" and another, from 1947, "Sun and Life". It is of course difficult to locate the precise source of this sexual energy; it resides, perhaps in the paintings' strange dense atmosphere, in their vibrancy and magnetism. Even her most innocent self-portraits have a peculiar electric charge that makes viewers pause in front of them in the same way that passersby were attracted to Frida's vital presence. Another part of the sexual charge lies in Frida's face - her penetrating, devouring glance beneath those hairy eyebrows, her carnal lips beneath a slight moustache. And, friends have noted, Frida's most passionate love affair was with herself. Indeed there is a strong element of self-fascinated autoeroticism in her display of wounds in paintings like "Remembrance of an Open Wound" and in other later wounded self-portraits.

Hayden Herrera, "Frida", 1983.

In 1937 Frida Kahlo painted "Memory" (or "The Heart"), oil on metal, one of her most famous paintings. It is a triple image of terrible injury, both physical (limb amputations) and psychological (excised heart). The work reflects her pain following the separation from her husband Diego Rivera. It is an image of hopelessness. But by the following year, Frida had changed direction. Her physical wounds, a result of polio of her leg she had contracted as a child, as well as a horrific bus accident that almost claimed her life in 1925 and which left her with life-long deformities and chronic pain, and her psychological pain a result of her broken marriage, betrayal by her sister, and her inability to bear children, remained with her, however her attitude towards these torments had hardened. Determined not to let life's tragedies overwhelm her, she looked to positive pursuits to distract her, if not to heal her, then at least to help her cope. She embraced her socialist politics, her love of animals, her pre-Colombian heritage, a

multitude of both heterosexual and lesbian lovers, her house and her gardens, but above all it was her Art that saved her. Not all pursuits were positive however; increasingly she would also take to strong alcohol and to opioids. Amalgamated within all of these, she maintained a vibrant joie de vivre, which included a heightened sense of traditional Mexican black humour, and an alarming modus operandi of outrageous sexual flirtation.

Her powerful sexual allure and even exhibitionism was a trait that was noted as early as her time in America. She especially used to like to tease the New York Press. For one particular mass interview, she received the reporters whilst in her bed, quite shocking in the context of the 1930s. Between answering their questions she provocatively sucked on a long candy stick. Her friend Suzanne Bloch, daughter of the Swiss composer Ernest Bloch was present at the interview and witnessed the embarrassed looks on the faces of the reporters. "She then stuck it under the bedcovers", Suzanne later reported, and to the further discomfort of the reporters, "She raised it up slowly", all the time firmly fixing their gaze with a totally expressionless face. She secretly delighted in their horror and Suzanne's blushes. One journalist later asked her "What does Mr. Rivera do in his spare time?". "Make love" she answered without batting an eyelid. This may have caused the journalist some embarrassment, but it was an accurate enough answer.

Outrageous flirtation was one thing in an age before media interviews were filmed, but Frida proceeded to record her antics for posterity in her paintings. It was a risky side to her work, many of her paintings could not be shown in public for decades. One such work which was actually controversially shown in 1938 was "Remembrance of an Open Wound", oil on canvas. It depicts her physical injuries, but unlike "Memory" of the previous year, there is a mischievous dark humour and sexual innuendo that seems to say, she finds it all a great laugh now. "Remembrance of an Open Wound", was lost, destroyed in a fire, we only know what it looked like from a single old black and white photograph that was taken of it. What has remained to posterity, however, is a preparatory sketch, "Self Portrait Showing the Scar". Unlike "Memory" where her heart has been torn from her chest, here her heart is back and whole again. Frida now takes strength from her work.

"Remembrance of an Open Wound", was purchased by American architect and author, Edgar Kaufman Jr. He recalled that the painting had "lyrical bright Mexican colours; pink, red, orange, black", and that, "you somehow felt that (her) pain and joy were indistinguishable!". In contrast to the despair of "Memory" Frida is now outrageously perverse. She sits with her legs apart, hitching her Tehuana skirt up over her thighs to display to the viewer her wounds. Her right foot (the work is done from a mirror image) is bandaged and propped up on a stool, an allusion to her deformed leg that she acquired as a result of childhood polio. It's a startlingly self-confident image, considering that in public she usually went to great lengths to hide her leg under long Tehuana skirts. It is a courageous self reflection, considering the public humiliation she suffered at the hands of Lupe Marín, one of Diego's ex-wives, on the day of her wedding celebrations. It was, being Mexican, of course a riotous affair. Diego had invited his ex-wife, who appeared to hold no rancour towards Frida, and Frida herself had not minded. But as the tequila began to flow more liberally, Lupe suddenly strode over to Frida, and in a rage lifted her skirt to reveal her deformed leg to all. She screamed out, "You see these two sticks? These are the legs that Diego has now, instead of mine!". Lupe, by all accounts, had spectacular legs. Then she stormed out. Diego had had so much to drink he merely

thought the whole episode a tremendous “joke”. Frida burst into tears and went home to her parent’s house and would not see Diego for several days.

If all this wasn’t enough self-exposure, then a second wound Frida displays is far more sinister, and even more personal. A long gaping laceration is seen high on her inner thigh. This open wound actively gushes blood onto her pristine white petticoat. It was not a real wound she had ever sustained, but rather alludes to (and draws the eye towards) her vagina which did sustain a horrible injury when she was impaled thorough the pelvis by a handrail, in the bus accident that almost killed her in 1925. As a consequence of this Frida could not bear children, a psychosocial torment that was far greater than any physical pain she would ever have.

Arising from the gash (in the lost completed work) is a leafy plant, a symbol of new life, an allusion to that fact that her fertility has been compromised. This wound can also be read as a sexual injury in the sense of her separation from her husband. But Frida, unlike “Memory” does not wallow in self-pity, rather she makes light of her situation. She once candidly told male friends, that the way she depicted her hand, placed over her lap and hidden behind her skirt, was meant to show that she was masturbating, even while she unabashedly gazes straight faced at the viewer, echoing her risqué New York bedroom interviews.

“Memory” recorded the agony of her husband’s affair with her own sister, Cristina, but from this incident a much stronger Frida emerged. She now gains strength in making light of her vulnerabilities that had so upset her on her wedding day. “Remembrance”, Hayden Herrera explains, “shows that Frida transformed the open wound of jealousy and betrayal into a different kind of openness”. She is now a sexually free woman, a shocking (in the true sense of the word) flirt, who, for all her supposed “suffering” as she fixes our gaze, seems as if she is “about to wink”.

Frida Kahlo had more reason than most to suffer depression, yet she lived in an age which barely acknowledged the condition. Even so in the 1930s no effective therapeutic agents existed, and none would until the mid - 1950s, after Frida had died. In her day other non - pharmacological treatments had to be used. Though Frida increasingly self-medicated with strong alcohol and later in life, opioids, her most effective self-treatment was always her Art.

PAROXETINE

Introduction

Paroxetine (trade name in Australia, “Aropax”) is a selective serotonin reuptake inhibitor (SSRI) antidepressant agent.

It has the shortest half-life of the SSRIs, and has no active metabolite.

Paroxetine is indicated for **major depression** (as for all the SSRIs as a class), however it has a range of additional more specific indications including:

- Obsessive-compulsive disorder
- Panic disorder
- Generalized anxiety disorder
- Post-traumatic stress disorder
- Social phobia

The potential for withdrawal symptoms is thought to be greater with **paroxetine** than with other SSRIs.

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.

Paroxetine was introduced into medical practice in the United States in 1992.

Chemistry

Paroxetine is the hemihydrated hydrochloride salt of a phenylpiperidine compound.

It is a chemical structure that is unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic or other available antidepressant agents.

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
- Clomipramine
- 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

Paroxetine hydrochloride hemihydrate as:

Tablets:

- 20 mg.

Mechanism of Action

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

The antidepressant action of escitalopram is thought to be linked to the potentiation of serotonergic activity in the central nervous system (CNS).

The SSRIs do not block the reuptake of noradrenaline.

Pharmacodynamics

Paroxetine is effective in improving depression and suicidal ideation concurrently during the first few weeks of therapy.

Morning dosing with paroxetine does not have any detrimental effect on either the quality or duration of sleep. Moreover, patients are likely to experience improved sleep as they respond to paroxetine therapy.

Where it is clinical practice to co-prescribe short acting hypnotics with antidepressants, no additional adverse events have been recorded.

Paroxetine in addition to its significant antidepressant effects, can also improve associated symptoms of anxiety.

Pharmacokinetics

Absorption:

- Paroxetine is administered orally.

It is well absorbed, but has extensive first-pass metabolism in the liver.

Distribution

- Protein binding is around 93 - 95%
- Paroxetine can cross the human placenta.
- Paroxetine is distributed into human breast milk in small amounts only.

Metabolism and excretion:

- Paroxetine is extensively metabolized in the liver.

It has the shortest half-life of the SSRIs, and has no active metabolite.

The metabolism of paroxetine is initially by the CYP2D6 system which can become saturable with increasing dose and increasing duration of treatment.

At steady state, when CYP2D6 has become saturated, paroxetine clearance is via an alternate pathway involving the P450 isoenzymes which, unlike CYP2D6, are not saturable at clinical doses.

Because of the involvement of CYP2D6 in the metabolic clearance of paroxetine, considerable variation can occur in the plasma concentrations achieved between individuals. However, there does not seem to be a clinical correlation between paroxetine plasma concentrations and clinical effect (or adverse experiences and efficacy).

Indications

Indications include:

1. Major depression (as for all the SSRIs as a class).

And specifically for paroxetine:

2. Obsessive-compulsive disorder
3. Panic disorder
4. Generalized anxiety disorder
5. Post-traumatic stress disorder
6. Social phobia

Contra-indications/precautions

Contra-indications/precautions to the SSRIs as a group include:

1. Known hypersensitivity to paroxetine or to other SSRIs
2. Caution with other **serotonergic** agents:
 - Co-administration 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:

- Hepatic impairment further increases the long half-lives of fluoxetine and its active metabolite, norfluoxetine; consider using an alternative SSRI, e.g. citalopram, or use a lower dose and titrate cautiously e.g. 10 mg once daily or 20 mg on alternate days, and titrate cautiously.

5. QT prolongation:

- QT prolongation can occur with fluoxetine treatment.

Fluoxetine should be used with caution in patients with conditions such as congenital long QT syndrome; acquired long QT syndrome (e.g. due to concomitant use of a drug that prolongs the QT).

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

Paroxetine is classified as a category D drug with respect to pregnancy.

Category D drugs are those drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialized texts should be consulted for further details.

Most studies have shown that there is no significant increased risk of congenital malformations following maternal use of selective serotonin reuptake inhibitors (SSRI) in early pregnancy. However, based on a preliminary analysis of data from a large study conducted in the United States, paroxetine has been found to increase the risk of congenital malformations such as cardiovascular malformations in infants. Information from the manufacturers also confirmed this increased risk.

Although the absolute risks associated with cardiac defects appear small in comparison to the baseline risks for the general population, consultation with a perinatal psychiatrist is recommended if the initiation or continuation of paroxetine therapy is required during pregnancy.

When patients present prior to conception or during the first 13 weeks of pregnancy, consider an alternative medicine to paroxetine. However, switching or changing antidepressants always carries the risk of relapse. If discontinuation of paroxetine is not possible, then a careful antenatal examination, including a detailed ultrasound at the 18th to 20th week of gestation, looking specifically for the presence of cardiac defects (e.g. ventricular septal defect) is recommended.

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.

Maternal use of SSRI has been associated with neonatal withdrawal symptoms, especially in late pregnancy. These symptoms include respiratory distress, irritability, temperature instability, sleep disturbance, tremors, jitteriness, feeding difficulties and diarrhoea, which can be attributed to serotonergic hyper stimulation.

Persistent pulmonary hypertension of the newborn (PPHN) is a rare condition, defined as a failure of the pulmonary vasculature to relax after birth with hypoxemia as a result. PPHN can be the result of various underlying pathological conditions. The evidence concerning the association between PPHN is still insufficient to contraindicate the use of SSRI during pregnancy.

Inform neonatal care providers about maternal use of paroxetine as adverse effects or withdrawal symptoms may be present in the newborn and supportive care may be required.

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

Based on limited studies, small amounts of paroxetine are excreted into breast milk, but no serious harmful effects have been found in breastfed infants.

If paroxetine is the medicine of choice, use the lowest effective dose and closely observe the breastfed infant for adverse effects such as excessive drowsiness, 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 neurodevelopmental outcomes of infants exposed to paroxetine via breast milk.

Adverse Effects

Adverse effects of the SSRIs as a group include:

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:

- **Citalopram** (and its (S)-stereoisomer or left-enantiomer, **escitalopram**) are more likely among the SSRIs to cause **dose-dependent QT prolongation**.

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:

Major depression:

- Oral, 20 mg once daily,

Gradually increasing as necessary to a maximum of 50 mg once daily.

Use of maintenance doses > 20 mg is not routinely necessary.

Generalised anxiety disorder / social phobia / post-traumatic stress disorder:

- Oral, start at 10 mg once daily,

Increasing if necessary to 20 mg once daily after a week.

Use of maintenance doses > 20 mg is not routinely necessary.

Obsessive-compulsive disorder / panic disorder:

- Oral, 20 mg once daily,

Gradually increasing if needed, up to 50 mg once daily.

Elderly / severe hepatic impairment / CrCl <30 mL/minute:

- Oral, consider an initial dose of 10 mg once daily.

Maximum dose is 40 mg once daily.



“Remembrance of an Open Wound” or “Self Portrait Showing the Scar”, black and white photograph of a lost original, oil on canvas, 1938, Frida Kahlo.

References

1. eTG - July 2019
2. Paroxetine in Australian Medicines Handbook Website July 2019.
3. Paroxetine in MIMs Website, 1 October 2017.
4. Paroxetine in RWH Pregnancy & Breastfeeding Guidelines; 7 May 2019.

Dr J. Hayes
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