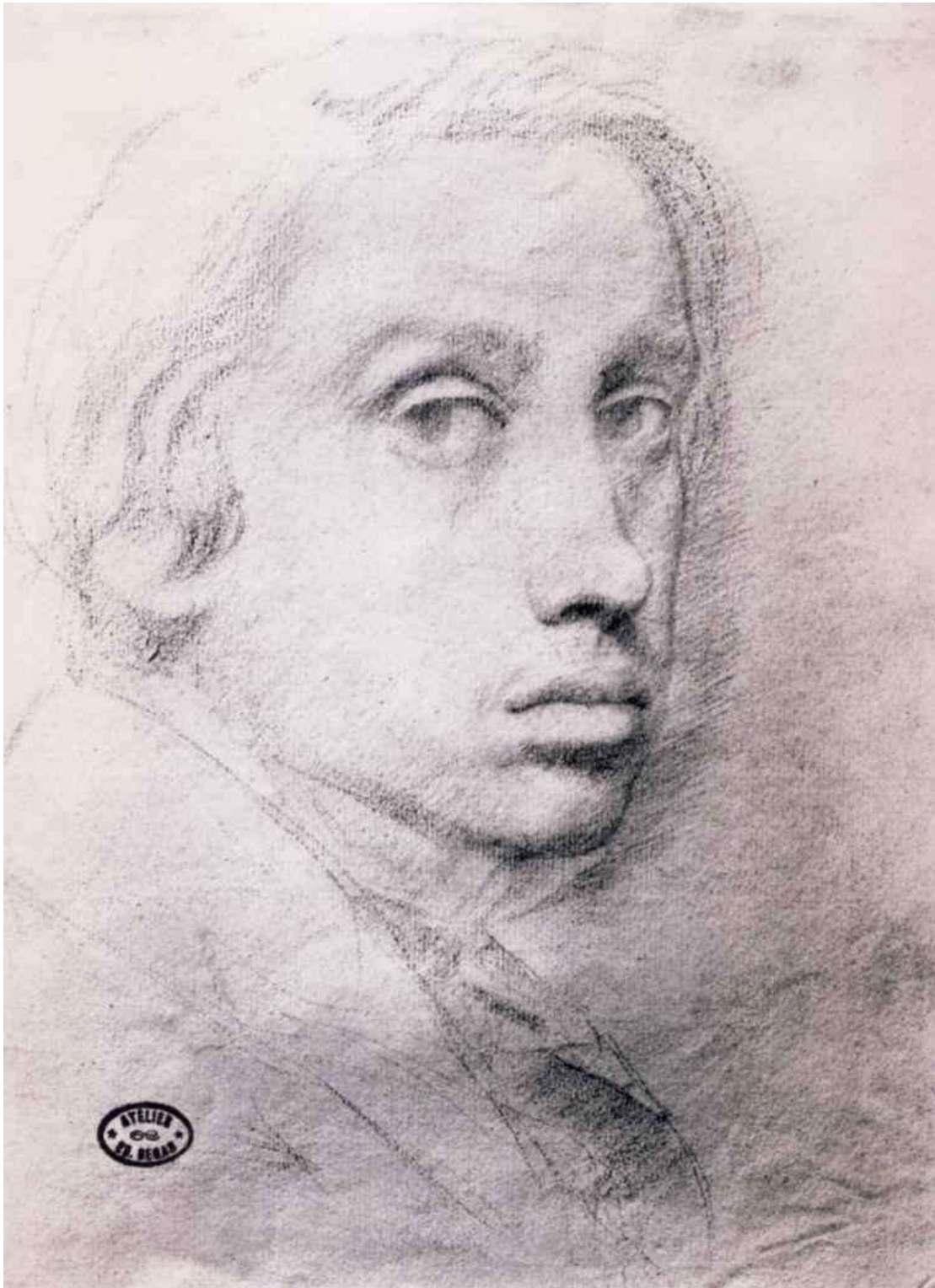


ESCITALOPRAM



Study for Self Portrait, pencil and charcoal on paper, Edgar Degas, 1855

What Edgar does not tell Mary....

That sometimes he cannot sleep at night because he is dreaming of gouache, lithography, pastel, monotype, charcoal, oil, etchings, plates, wax. That he wants to stop and start time at his prerogative so that he can revel in the bounty of materials, van challenge himself and experiment without time passing because the day isn't long enough. That the circus or the Opera ballet, or the cafe chantants or dinners with friends or the delicious masculine embrace of the racetrack devour his evenings and Sundays but in between there is only work. That some days he looks up and hours have passed and he is late for one thing or another and he races to the cafe or the friends or the theater and what he leaves behind is unfinished work, and he thinks nothing he makes will ever be finished. That he must make careful calculations in order to produce his articles because he is not gifted, he is not prescient, he is not an auteur, he is only a draftsman, a servant, a plodding poseur who wishes to excel. That he is hampered by the infernal blur in his eye he fears will only spread. That the arrangement of legs on a group of dancers or the colour of skirt sashes or the depth of the stage or the bend of a laundress's back or the line of her apron confounds him and has to be worked and reworked.

That these problems haunt him, and he fears that he has lost his touch. That he has to struggle with each canvas, though he has already painted many. That with each beginning he is again a beginner. That each composition requires its own rules. That his experienced, yet flawed eye needs repetitive correction. That colour is still changing, though no one believes him and no one believes that what he sees and what he used to see are so different that it is as if he were seeing the world through and ever-changing, ever blurring, ever-achromatic prism. That the Sturm und Drang about their annual exhibition is always a struggle when people - Renoir, Monet - defect to the salon seeking its false external confirmation, hoping to find in the cloistered snobbery some validation, when validation ought to be internal, personal, private, and he can't understand why they done believe in themselves. That art is a confection - it is true only when it is false - and their attempt to render natural light negates the filter and the eye and the brain.

That the endless haggling over apartment rental and lights and hanging takes up so much time that he thinks of never exhibiting again, but there is no economic salvation for the artist who does not show. That the inglorious details of buying and selling and the oppression of the Bank of Antwerp intrude and force him to ask Durand-Ruel for money in order to pay his house keeper, Sabine and to eat. That the process of selling art is so repugnant, so commercial, yet so necessary that he submits to it and tries to do so with integrity and inclusiveness, but the others like to complain and exclude artists they believe inferior, which is just like the Salon jury, but they can't see the hypocrisy because they are so taken up with themselves. That one must believe in oneself enough to attempt to surpass Rembrandt, or Ingres or Delacroix. That this striving is always on his mind, this making a mark, this elevation of art to the sublime, the real, the irrelevant, the necessary. That he is unequal to the task - every day, he believes this - and doesn't know where to place himself in the world or history or the future. The red herring of pride interferes with real work because the real work is lines and more lines and the willingness to stand before the canvas, the sculpture, the pastel, the subject, the window, the model and construct form and shape and light and colour. That such courage is only the beginning. That there is the essence of the thing that struggles to make itself known, and you don't know what it is when you begin,

that you discover it as you work. That is the secret that critics and laypeople do not understand. That nothing is clear to the artist until the art reveals itself and it is a mystery where art resides before it is expressed even though he can recount each step and each choice and each calculation he made, it is this riddle of art that eludes him, even as it infuses him as he works, even as he rejects it because he applies tenacious deliberation to his days and the tension between what he knows and what he doesn't know abounds. That he doesn't want to believe the muse exists, though she does - of course she does - for he cannot account for the music of his composition, even as he follows the golden ratio and the laws of tonality and perspective there is the in-between, wherein his brush works and colour plays and it is magical and true and beguiling and it comes from him and not from him. That he falls in love with every new confection and doesn't want to let it go, though he must, to pay bills, to live, to eat, to drink to go to the Opera, to travel, to buy oil, charcoal, paint, canvas, wax, fixatives, frames, nails, lumbar, saws, brushes, turpentine, poppy seed oil, needles, plates, silk, and now his latest, his most exciting: tulle and tarlatan and even a skein of real hair, and this new project - more than the etching, more than the puzzle of black and white that delights Mary Cassatt - absorbs him, and he would like to tell her that he is not fickle, and he is not flighty, that he is not mercurial, that he is helpless, that inside him is a pirate that plunders his desire and twists it and distracts him from a single scheduled purpose with deadlines and demands and expectations to explore the unexpected, the rare, the difficult, and he has already mastered the etching, so therefore it is boring. That he needs to prove himself only to himself. That work is never finished, because some other beguiling insight is always out of reach., lurking, taunting. That he defected because he has to make money, has to meet commissions, and he could not find the time to devote to his avowed goal of "Le Jour et la Nuit". That this is not true, not really, because the truth, ever elusive, is that he cannot slow down his mind for other people, nor for the arbitrary requests and obligations and responsibilities that he has imposed on himself, because deadlines are malleable, and he is sorry that he committed himself to Mademoiselle Cassatt and that she believed him and made a religion of the print and paper and the press but he is past that now, or not yet ready, or the process no longer intrigues him, all possibilities that he cannot parse, not for her not for anyone, not for himself. That the conundrum is that he is who he is, and this defection is not personal or disloyal or a breach of trust. That the non-elusive truth is that she had never failed him. That he can't think of a moment or gesture or an act wherein she betrayed or disappointed him. That even her anger over Berthe was an attempt to persuade him to kindness. That she cheers him, she delights him, he respects her. That she looks at him sometimes as if she sees through him, but he knows himself to be opaque, because he has painted himself that way, and it is only her desire that makes her believe she understands him, when even he cannot escape the murky dungeons of his own soul.

Robin Oliveira, "I Always Loved You", Viking, 2014

Cutting edge Psychiatry in the last quarter of the Twentieth century pronounced dogma that so-called "endogenous" (read "idiopathic") depression was simply a consequence of a "chemical imbalance" in the brain. Big Pharma was more than happy to oblige! Simply raise the levels of bioactive amines in that case and all will be well! But the human psyche is a far more complex entity than that - failure of a patient to admit to their innermost primal fears, emotions, apprehensions, anxieties - even to themselves - does not mean that they do not exist!

ESCITALOPRAM

Introduction

Escitalopram (trade name in Australia “**Lexapro**” among others) is a **selective serotonin reuptake inhibitor (SSRI)**.

The SSRIs in general are as effective as the first generation antidepressant agents for the treatment of depression (TCAs and MAOIs) although not nearly as lethal in overdose as those agents, nonetheless they are not without their own significant side effects.

In particular **citalopram** and **escitalopram** are more likely among the SSRIs to cause **dose-dependent QT prolongation**.

These two agents are also the most likely to cause **seizures**.

Citalopram is sold as a racemic mixture, consisting of 50% (R) (–) citalopram and 50% (S) (+) citalopram. Only the (S) (+) enantiomer has the desired antidepressant effect.

Escitalopram is the (S) (+) enantiomer of citalopram. Whether or not it has any particular superior therapeutic properties to citalopram or merely represents an example of Big Pharma “ever-greening” i.e a means by which a patent that is about to expire is extended in order to retain ongoing royalties from a product virtually indistinguishable from the original, remains a controversial point.

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 in 1986 became the first SSRI agent to be introduced into medical practice.

Citalopram was developed by scientists at the pharmaceutical company Lundbeck, also in 1972. It was introduced into clinical practice in 1989 in Denmark and in the US in 1998.

Escitalopram was developed in close cooperation between Lundbeck and Forest Laboratories in the 1997. The short time (3.5 years) it took to develop escitalopram can be attributed to the previous extensive experience of Lundbeck and Forest with citalopram. The FDA approved escitalopram for major depression in August 2002 and approved it for generalized anxiety disorder in December 2003.

Chemistry

Citalopram has one stereocenter, to which a 4-fluoro phenyl group and an N,N-dimethyl-3-aminopropyl group bind.

As a result of this **chirality**, the molecule exists in (two) enantiomeric forms (mirror images). They are termed S (+) citalopram and R (–) citalopram.

Citalopram is sold as a racemic mixture, consisting of 50% (R) (–) citalopram and 50% (S) (+) citalopram.

Only the (S) (+) enantiomer has the desired antidepressant effect.

Lundbeck markets the (S) (+) enantiomer, the generic name of which is **escitalopram**.

Citalopram is supplied as the hydrobromide whereas escitalopram is supplied as the oxalate salt (hydrooxalate).

In both cases, these salt forms of the amine make these otherwise lipophilic compounds water soluble.

Classification

The selective **serotonin reuptake inhibitors (SSRIs)** currently include:

1. Fluoxetine
2. Citalopram
3. **Escitalopram**
4. Fluvoxamine
5. Paroxetine
6. Sertraline
7. Dapoxetine

The **serotonin and noradrenaline reuptake inhibitors (SNRIs)** currently include:

1. Venlafaxine
2. Desvenlafaxine
3. Duloxetine

Preparations

Escitalopram oxalate as:

Tablets:

- 10 mg
- 20 mg

Oral liquid:

- 20 mg/mL (1 mg/drop), 15 mL

Mechanism of Action

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

They do *not* block the reuptake of noradrenaline.

Pharmacodynamics

Escitalopram is the active isomer of citalopram. No significant clinical advantage over the other SSRIs has been demonstrated

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

Pharmacokinetics

Absorption:

- Escitalopram is administered orally.

There is virtually complete absorption from the GIT

While the absolute bioavailability of escitalopram has not been studied, it is unlikely to differ significantly from that of racemic citalopram (i.e about 80 %).

Distribution

- The apparent volume of distribution ($V_{d,\beta}/F$) after oral administration is about 12 - 26 L/kg.
- Protein binding is around 55 %.
- Escitalopram can cross the human placenta.

- Escitalopram is excreted in human breast milk in small amounts.

Metabolism and excretion:

- Escitalopram is metabolized in the liver to demethylated and di-demethylated metabolites as well as an N-oxide metabolite.

Biotransformation of escitalopram to the demethylated metabolite is mediated by a combination of the CYP2C19, CYP3A4 and CYP2D6 systems.

- Approximately 8.0% of escitalopram is eliminated unchanged in urine
- Half life is about 30 hours.

Indications

The indications for escitalopram are essentially the same as for citalopram and include:

1. Major depression
2. Anxiety disorders:

Including:

- Generalized anxiety disorder
 - Social phobia
 - Obsessive-compulsive disorder (OCD)
 - Panic disorder
3. Bulimia nervosa
 4. Premenstrual dysphoric disorder

Contra-indications/precautions

These include:

1. Known hypersensitivity to citalopram or escitalopram or to other SSRIs in general
2. Drug interactions:
 - 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**.

- **CYP2C19 inhibitors:**

- ♥ Citalopram is metabolized by the CYP2C19 system: use lower doses if citalopram is combined with **an inhibitor** of CYP2C19 or there is a **genetic lack** of CYP2C19 activity as citalopram's concentration may increase and so may increase the risk of arrhythmia.

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:

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

This is greater in doses > 40 mg daily.

Citalopram 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. Age related:

- **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.

- **Elderly:**
 - ♥ Use lower doses as concentration and half-life are increased compared to younger people.

7. Bleeding risk:

- 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

Escitalopram is 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.

Pregnancy Summary

Escitalopram is the active S (+)-enantiomer of citalopram.

Most studies have shown there is no significant increased risk of congenital malformations following escitalopram use in early pregnancy.

However, newborns exposed to selective serotonin reuptake inhibitors (SSRI), especially in late pregnancy, have experienced self-limiting neonatal withdrawal symptoms.

These symptoms include respiratory distress, irritability, temperature instability, sleep disturbance, tremors, jitteriness, feeding difficulties and diarrhoea, which can be attributed to serotonergic hyperstimulation.

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 the maternal use of escitalopram as supportive care may be required.

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

Breast feeding

There is limited safety information available following the use of escitalopram in breastfeeding.

Very small amounts of escitalopram are excreted into breast milk, but no serious harmful effects have been noted in breastfed infants .

If escitalopram is the medicine of choice, use the lowest effective daily dose and closely observe the breastfed infant for adverse effects such as 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 neuro-developmental outcomes of infants exposed to escitalopram via breast milk.

Adverse Effects

These 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

Usual adult dosing is:

- Oral 10 mg once daily

Increased if needed after 2 - 4 weeks to a maximum of 20 mg once daily.

Maintenance doses >10 mg are not usually necessary.

For elderly / hepatic impairment:

- Adult, oral 5 mg once daily

Increased if needed after 2 - 4 weeks to a maximum of 10 mg once daily.

References

1. eTG - July 2017.
2. Escitalopram in Australian Medicines Handbook Website, Accessed August 2017.
3. Citalopram in MIMs Website 1 July 2016.
4. Escitalopram in RWH Pregnancy & Breastfeeding Guidelines, 3 November 2016

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