

SERTRALINE



Mother and daughter; Lwaxana Troi (Majel Barrett-Roddenberry) and Deanna Troi (Marina Sirtis), "Dark Page", 1993, "Star Trek, The Next Generation", created by Gene Roddenberry

CRUSHER: *Deanna, you understand that if your paracortical readings go too high again, I'm going to tell Maques to sever the connection.*

Deanna TROI: *I understand.*

(Troi in her mind now appears in a long dim deserted corridor of the Enterprise - she sees the small girl Hedril, who is petting a ferocious wolf!)

TROI: *Hedril, be careful. (Hedril continues to pet the wolf)*

HEDRIL: *Who is Hedril? - the image vanishes.*

TROI: *Wait! I want to talk to you. (Troi runs down the corridor but it ends in a vast abyss of dark space!)*

LWAXANA: *Help me. Help me! (she hears the tearful calling of her mother's voice. Deanna jumps into the black void)*

She now appears in the Enterprise's Greenhouse. Although the pond is still, the sound of running water is very loud. Deanna's reflection turns into that of a mysterious young blonde girl)

LWAXANA: *Go away, please ! (The image of Deanna's distraught mother, Lwaxana, appears).*

TROI: *Mother? (Desperate)*

LWAXANA: *Go away (Crying)*

TROI: *No! I want to help you! Why did you delete parts of your journal? Did something happen to you you don't want me to know about?*

LWAXANA: *Leave me alone, please (sobbing)*

TROI: *Who's Hedril, mother? Why is she here? Is Hedril **me** when I was a little girl?*

LWAXANA: *No! Oh, no, I'd never let anything happen to you. Never!*

TROI: *Did you let something happen to someone? Was it here at El'nar?*

LWAXANA: *You were just a baby!*

TROI: *Tell me. Whatever it is. We can face it together.*

LWAXANA: *I can't. I can't ! (sobbing now, uncontrollably)*

TROI: *You can! We can together! (An image of Hedril reappears)*

HEDRIL: *Help me. Help me, papa. (an image of Deanna's long dead human father, Ian, appears. Hedril and Deanna's father are playing with a small dog by the pond, while a baby is sitting nearby).*

LWAXANA: *Please! Don't make me go through this again, (turning her face away from the images).*

IAN: *Hold on to the dog now, don't let him run off. (an image of Lwaxana as a young woman has now joined those of Ian and the mysterious little girl)*

HEDRIL: *I won't. Mommy, can we go play by the water?*

LWAXANA: *No, **Kestra**, stay here with us, (Lwaxana now refers to the image of Hedril as "Kestra")*

HEDRIL/ Kestra: *Please? (the baby begins to cry now)*

LWAXANA: *Kestra. Oh, Kestra, you've made the baby cry.*

TROI: *Kestra? Mother, who is Kestra?*

LWAXANA: *Don't cry, Deanna. Don't cry, mommy's here.*

*(Troi is shocked - The baby is **her**. Kestra is her older sister!)*

HEDRIL/ Kestra: *Mommy, please?*

IAN: *No, Kestra. We're going to eat in just a few minutes.*

LWAXANA: *What's wrong, what's wrong, little one? Tell mommy what's wrong. Ian, she's teething, Now where's her ring?*

(Then Darkness)

LWAXANA: *No, no. I don't want to see this again. I can't!*

TROI: *What happened, Mother. What happened next? (Frantic)*

LWAXANA: *I don't remember.*

TROI: *You have to. You can't hold it back. It's killing you!*

LWAXANA: *The dog got away....She ran after him....We didn't notice.*

(Images re-appear: Ian is soaking wet and Lwaxana is distraught)

LWAXANA: *Why? Why did I look away? Why wasn't I paying attention?*

(Lwaxana is inconsolable. Troi now realizes that Kestra has drowned in the pond)

TROI: *(Crying) You have to forgive yourself, Mother. You have to let go.*

LWAXANA: *How can I? I let her die.*

TROI: *It was a terrible tragedy. The worst thing that can happen to any parent. I know you feel responsible but it was an accident. And what you're doing isn't fair to Kestra. I saw a little girl who was sweet and happy. She must have brought a great deal of joy to your lives.*

LWAXANA: *(Settling) She woke up every morning with a smile.*

TROI: *Isn't it better to remember her like that? I just found out I had a sister I never knew! (crying) I'd like to learn what was good and joyous about her. To celebrate her life, not mourn it.*

LWAXANA: *How? How can I do that?*

TROI: *Kestra was here a few moments ago. Bring her back Talk to her.*

LWAXANA: *No. No.*

TROI: *Do it, mother. Tell her how you feel. I'll be here with you. I'll help you.*

KESTRA: *(Image of Kestra appears) Mommy?*

LWAXANA: *Kestra. Oh, Kestra. My precious one. I'm so sorry. (They embrace)*

KESTRA: *I have to go now.*

LWAXANA: *I know. I know, (tearful, but calm now).*

(Kestra vanishes, and Lwaxana takes Deanna's hand - Lwaxana and Troi emerge from their subconscious dream state back into the real world. They are holding hands as they both wake up)

(Later, in Troi's quarters - Lwaxana has dug out a picture of Ian with the two girls)

LWAXANA: *I remember the day I took this. Mister Homn said he saved it in case someday you wanted to see her. I wish you could have known her, Deanna. I wish you two could have grown up together.*

TROI: *Tell me about her....I want to know everything.*

*The United Federation of Planets is desperate to establish an alliance with an alien humanoid species, known as the Cairn. The only problem, however, is that the species is “empath”, that is they communicate with each other by mental telepathy. This is not a unique ability in the Galaxy, indeed one humanoid species, the Betazoids are part of the Federation, though their telepathic abilities are limited, they communicate both verbally and by telepathy. They can only sense emotional states in humans, rather than read their thoughts. The unique thing about the Cairn is that they **only** communicate by telepathy. This incredible evolutionary pathway however meant that they have virtually lost any ability to verbalize at all. The Federation has only been able to communicate with the Cairn via their partial empath allies, the Betazoids, who can still only communicate with them with great difficulty.*

Negotiations have reached a critical point. A high-council of the Cairn has beamed aboard the Enterprise, where the conditions for formal entry into the Federation are to be established. One of the most skilled Betazoid empaths in the Federation, of suitable rank, Lwaxana Troi, happens to be the mother of the Enterprises’ chief councillor, Deanna Troi. Weeks of sustained empathic communication however, begins to take its toll on the mental stability of Lwaxana. The Cairn communicate with each other totally, that is nothing, not even the darkest secrets can be kept from each other, there is total and brutal honesty between them, however Betazoids, like humans, prefer some things of their personal life to remain private. Lwaxana must use all her mental strength to keep her private thoughts from being probed by the Cairn. The Cairn become frustrated by what they can only barely verbally communicate as Lwaxana’s “dark places”. Although frustrated the Cairn are understanding and do respect the right of privacy when this unknown entity is carefully explained to them, even though they do not fully understand it. Suddenly disaster strikes! The mental strain becomes too much for Lwaxana and she collapses into a profoundly catatonic state. She is taken to sick bay, where Dr Crusher announces that her condition is beyond anything known to her, yet one thing is certain. Lwaxana Troi is dying of some kind of Betazoid status epilepticus!

Maques, the chief of the Cairn delegation, who has brought his young daughter, Hedril, with him, becomes seriously alarmed for Lwaxana. He announces in very broken words that he believes that Lwaxana’s state is somehow connected to her “Dark Place”. The only way to save Lwaxana is by rescuing her from it. It could be very dangerous he says, but he can use his astonishing empathic powers as a conduit for another Betazoid to enter Lwaxana’s mind. Deanna, Troi, beside herself with grief, volunteers immediately to try. Maques sets his mind to work - suddenly Deanna finds herself in a dreamlike world - her mother calling out to her in melancholic desperation. Deanna discovers her mother’s darkest most anguished secrete subconscious place - the accidental death by drowning of the solder sister she never knew she had. Lwaxana by sharing her dark place finally attains peace. They both awake with tears in their eyes, holding each other’s hands.

Mid-Twentieth century medicine developed the concept that psychiatric illness is nothing more than “chemical imbalances”. Big Pharma was more than happy to agree and drove a massively profitable pharmaceutical industry off the back of these new and most convenient theories. But the human psyche (as well as Betazoid psyche) is a far more complex entity than a mere “chemical imbalance”. There are dark places in everyone’s psyche, that cannot be reached by the mere tweaking of biochemical neurotransmitters.

SERTRALINE

Introduction

Sertraline (trade name in Australia “**Zoloft**” 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.

Sertraline was approved for clinical practice in the UK in 1991

It was approved by the U.S. Food and Drug Administration (FDA) in 1991

It entered the Australian market in 1994 and by 1996 it was the most prescribed antidepressant.

Chemistry

Sertraline is chemically unrelated to tricyclic, tetracyclic or other previously developed antidepressant agents.

It is a disubstituted tetra-hydro-naphthalene.

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

Sertraline as hydrochloride 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

Sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on noradrenaline and dopamine neuronal reuptake.

Antagonism of muscarinic, histaminergic and alpha1-adrenergic receptors have been hypothesised to be associated with various anticholinergic, sedative and cardiovascular effects of classic tricyclic antidepressant drugs. Sertraline 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.

The onset of therapeutic effect may be seen within **7 days**; however for full activity **2 - 4 weeks** are usually necessary for depression.

If no effect is apparent after 6 - 8 weeks, discontinuation of the treatment should be considered.

Pharmacokinetics

Absorption:

- Sertraline is administered orally.
- It undergoes extensive first pass metabolism.

Distribution

- Sertraline is highly protein bound, around 98%
- Sertraline can cross the human placenta
- Sertraline is excreted into human breast milk.

Metabolism and excretion:

- Sertraline is metabolized to N-desmethylertraline
- The average terminal elimination half-life of plasma sertraline is long at about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one week of once daily dosing.

Indications

Indications include:

1. Major depression
2. Obsessive-compulsive disorder
3. Panic disorder
4. Social phobia
5. Premenstrual dysphoric disorder
6. Bulimia nervosa
7. Post traumatic stress disorder

Contra-indications/precautions

These include:

1. Known hypersensitivity to sertraline 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

Sertraline is a classed 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.

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.

However, newborns exposed to 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.

Neonatal care providers should be informed about the use of sertraline as potential adverse effects or withdrawal symptoms may be presented in newborns.

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.

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

Breast feeding

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

Some clinicians consider sertraline one of the preferred antidepressants in breastfeeding as its levels in breast milk are low. (*AMH for citalopram, AMH Website, Accessed August 2017*).

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

Dosing²

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.

Major depression:

Adult:

- Oral 50 mg once daily

Gradually increase as necessary to a maximum of 200 mg once daily.

Use of maintenance doses > 50 mg is not routinely necessary.

Obsessive-compulsive disorder:

Adult, child > 12 years:

- Oral, 50 mg once daily.

Gradually increase as clinically indicated to 200 mg once daily.

Panic disorder, social phobia:

Adult:

- Oral 25 mg once daily

Increase if necessary to 50 mg once daily after a week.

Use of maintenance doses > 50 mg is not routinely necessary.

Premenstrual dysphoric disorder:

Adult:

- Use the lowest effective dose and reassess need for continued treatment regularly.

Some women may need higher doses.

Continuous treatment, oral 50 mg once daily.

Cyclic treatment, oral 50 mg once daily starting 14 days before the anticipated start of menstruation until the first full day of menses.



Help me Deanna. Help me!

References

1. eTG - July 2017
2. Sertraline in Australian Medicines Handbook Website Accessed May 2017.
3. Sertraline in MIMs Website, 1 November 2016.
4. Sertraline in RWH Pregnancy & Breastfeeding Guidelines; 9 February 2017.

Dr J. Hayes
April 2018