Dosage, effect and points to consider when starting an SSRI

Introduction

Former neuropsychiatrist Carla Rus and former nurse Idelette Nutma (manager of 'Sepsis en daarna') started a collaboration in January 2022 to provide patients with Post-Covid Syndrome (hereinafter referred to as PCS) with good information about SSRI medication to treat their complaints. In her long career, Carla Rus has already gained a lot of experience with the use of SSRI medication for ME/CFS. Because there is a lot of overlap with the complaints of PCS, she has also started to advise SSRI medication in a number of PCS patients to see whether they too could benefit from this. A two-thirds of the patients reported positive effects, resulting from fairly good to large improvements. Some PCS patients were subsequently able to (partially) resume their work. As a result, Carla Rus decided to make this more known and at the same time call for a large study (an RCT) to further investigate these effects and gain more insight into the question: for which PCS patients does the drug work, based on which mechanisms of action, and for which of them does it not work?
Because there was no RCT yet, we decided to conduct an exploratory study as a first step towards an RCT. This is partly qualitative and partly quantitative research. PCS patients who had reached out to us asking if they could participate in this research were asked to complete a questionnaire with open, structured and semi-structured questions.

On November 2, 2023, the results of this first pharmacogenetic intervention with positive results will be published in Science Reports: 'Treatment of 95 post-Covid patients with SSRIs'

Results

After treatment with an SSRI, 7.5% reported a 'strong' improvement, 29% a 'good' improvement and 27% a 'fairly good' improvement. 26.9% noticed a slight improvement and 9.7% saw no change. The effect of the treatment appears to differ per symptom. Brain fog and overstimulation improved the most, followed by fatigue and heart palpitations, while muscle complaints improved the least.

Side effects

31.6% initially experienced serious side effects, 54.7% mild, and 13.7% no side effects. In 79.2% with side effects, these reduced or disappeared within a few weeks. When patients reacted strongly lowering of the dosage and/or a switch to another SSRI was recommended.

Background information in advance

It is important to mention that SSRI medication for PCS complaints is used here for other complaints than depression. The researchers have indications that post-Covid syndrome is accompanied by a dysregulated interaction between the immune system and various neurotransmitter systems (deduced from the effect and knowledge of SSRI medication to date). SSRI medication is used to influence, among other things, the inflammatory response in the brain, the hormonal axis in the brain that stimulates cortisol production in the adrenal glands and the control of the autonomic nervous system. Carla Rus proposes the hypothesis that SSRI could mean something for PCS patients based on the scientific literature and the insights previously gained from the development and action of this medication. This is also supported by, among others, the publication in 'Cell' on October 16, 2023, entitled: “Serotonin reduction in post-acute sequelae of viral infection” which shows that a post-Covid patient has on average only half the serotonin compared to healthy subjects. The Cell research also shows that sick mice recovered from an SSRI. Furthermore, our hypothesis is supported by research that concludes that an important immunological pathway - which, like the serotonin pathway - uses the building block tryptophan, is overactive in PCS. See further under 'Mechanisms of action' for an overview of all points of action that may provide an explanation for the effect of SSRI medication.

Carla Rus and Idelette Nutma make every effort to provide clear information and advice with which PCS patients can go to their treating doctor. The patient and the treating physician decide together and the responsibility for the treatment naturally lies with the treating physician. Carla Rus is always open to consultation with the latter if desired.

Effect of SSRI medication

The effect takes effect after 2 - 4 weeks, after which the effect can increase even further. The effect may also take longer to occur; sometimes it takes 6 - 8 weeks.
If the patient still experiences improvement after increasing the dose, (of course, cautious) increasing the dose is fine. However, if the side effects become stronger and/or there is little improvement, it is wise to maintain the dose at the level at which the effect makes a significant difference for the patient and he/she can manage with as little medication as possible.
*See page **5** and **6** for further details on building up the medication as well as for explanation about the side effects.*

Sometimes the improvement led to patients getting back on their feet after 2 years of being in a disabling situation. The responses in general of PCS patients show that the following improvements can occur after starting an SSRI (the extent to which varies per patient):

- Significantly reduced or disappeared brain fog
- Significant decrease in neurocognitive complaints (problems with memory/concentration)
- Decrease in overstimulation
- Increased energy
- More stability in mood and energy
- The problems with an excessively elevated resting heart rate also often decrease
- Reduction of headaches
- Decrease in muscle pain and muscle weakness

Decrease in PEM (unfortunately we did not measure this separately, but it clearly emerges from the open question. Many also included it among 'other complaints' that later decreased).

Possible mechanisms of action

– 1. **Dysregulation of the tryptophan system**. The overactive kynurenine pathway absorbs more than 95% of the tryptophan in PCS. Research shows that the amount of tryptophan in blood is decreased in PCS patients.

An overactive KP during a severe infection however, is toxic for neurons, especially for serotonin neurons. Not only does the KP hijack tryptophan away from the serotonin pathway, the metabolite kynurenine and oxidative stress also lowers the level of tetrahydrobiopterin (BH4), an important coenzyme of the serotonin pathway. Moreover, BH4 is an important coenzyme of the dopamine pathway – and to the norepinephrine pathway – thus the overactive KP damages these two neurotransmitter systems too. When there is no longer enough tryptophan, this can lead to serotonin depletion.

SSRI's make the serotonin in the neurons more available through inhibition of reuptake and can partly compensate for the deficiency of tryptophan. Moreover, SSRIs lower oxidative stress. That could be an explanation for our finding that PCS patients often have fewer complaints due to SSRIs. But that may come to an end when all the serotonin from the neurons is in the synapses. Nevertheless, after half a year or more (in this research 24 patients), many people still felt good when using an SSRI. So we can (hypothetically) conclude that an SSRI probably indirectly contributes to – when there is a lack of serotonin in the neurons – that these neurons start to pull harder on the available tryptophan. So SSRIs could slow down the overactive KP. There is no theoretical argument against this hypothesis. Read more under the topic '**Supportive nutritional supplements**'.

–2. **Disrupted HPA axis**. In PCS, the hypothalamic-pituitary-adrenal axis (HPA axis) is disturbed. As a result, people with PCS only have 50% of their normal cortisol levels. Having enough stress hormone cortisol is necessary to have enough energy during the day to live. An SSRI restores this HPA axis to a greater or lesser extent.

–3. **Disrupted brain stem**.
The brain stem, the oldest part of our brain, is responsible for basic functions such as body temperature, sleep-wake rhythm, heart rate, breathing, blood pressure, digestion, eye movements, urination, hearing, tasting, chewing, swallowing, and feeling movement and gravity. Neurotransmitters that are especially important there include serotonin, norepinephrine and dopamine. The serotonergic neurons start in the raphe nuclei in the pons and may exert their influence there.

–4. **Disrupted autonomic nervous system (ANS) balance.**
An SSRI has a beneficial effect on disturbances in the autonomic (involuntary) nervous system. Such as through influence on pontine nuclei as part of the reticular ascending system (formation reticularis). Therefore, an SSRI can also play a role in the treatment of dysautonomia in PCS.

–5. **CNS symptoms**
Brainfog and sensory overload responded best to treatment with an SSRI. The raphe nuclei (pons) in the brain stem is the location of the origin of the serotoninergic system. From there, axons are sent throughout the CNS.10 So SSRIs can intervene throughout the whole brain. Dissociative symptoms also disappeared. In sensory overload and dissociation, there is sensory overload due to lack of filtering. The primary unimodal sensory brain regions do not cooperate well with the associative sensory brain regions. It is known that an SSRI can sometimes help with this. Many PCS patients struggle with forgetfulness.1 In the hippocampus, the control centre of memory, serotonergic neurons are dominant. SSRIs also stimulate the production of serotonin cells in the hippocampus. Possibly partly because of this, the patients'
forgetfulness decreased.

– 6. **Sigma1 receptor agonist**
The SSRIs fluvoxamine and fluoxetine have been shown to have extra anti-inflammatory effects during Covid-19 infection by inhibiting sphingomyelinase acid (ASM).33 Furthermore, an SSRI reduces the pro-inflammatory cytokines Interleukin 2 (IL 2) and IL 17 in the CNS. In this case, the SSRI may be a sigma1 receptor agonist.

– 7. **Positive influence of SSRIs on the circulatory system.**
Many Covid-19 and PCS patients have microclots indicative of coagulation problems. Microclots impede oxygen and nutrients flow to organs and tissues.8 Platelets are

involved in clotting. Platelets transport serotonin, because serotonine has a function in clotting. With serotonin deficiency, platelets become less functional. Because SSRIs inhibit the reuptake of serotonin in platelets, they prolong clotting time and could theoretically dissolve microclots. But an SSRI can benefit blood circulation in other ways, too. SSRI medication may show an anti-inflammatory effect on endothelial cells. SSRIs reduce the expression of cytokine-induced endothelial adhesion. This makes it difficult for circulating adhesion molecules, such as monocytes, to adhere. This mechanism may partially explain their cardioprotective effects.

Points of attention

Types of SSRI and their effect

Citalopram, Escitalopram, Fluvoxamine, Fluoxetine and Venlafaxine can all be used, but Venlafaxine and also Fluvoxamine initially cause stronger side effects in some PCS patients.

Important: because Fluvoxamine can cause quite strong side effects, half a starting dose and increasing (and later reducing!) in smaller steps is recommended. For tapering off schedules, see the link under the topic 'Passing off' below.

Important: Venlafaxine works in the same way, but in a slightly higher dose also through a different route, via the dopaminergic metabolism; therefore, it has a very powerful effect. Build up extra carefully.

Important

Regarding other types of SSRI medication, it is good to distinguish between **ant**agonists and **a**gonists of the Sigma1 receptor.

Citalopram, Escitalopram, Fluvoxamine and fluoxetine are agonists of the Sigma1 receptor

– Sertraline is antagonist

– Paroxetine does not have a significant effect on the Sigma1 receptor.

– Citalopram, Escitalopram and Fluoxetine are similar to Fluvoxamine in this respect.

Venlafaxine is not actually an SSRI, but an SNRI. Therefore, this medicine stimulates noradrenergic metabolism more than SSRIs. In this context we would also like to mention Duloxetine (like Venlafaxine, also an SNRI) because this can be considered in patients with serious muscle complaints. Some patients who were prescribed this by their treating physician reported a significant decrease in muscle pain**.**

Side effects (general)

The side effects are described in the prescription and may include fatigue, disturbed sleep, headache, dry mouth, dizziness, gastrointestinal disorders. Mental effects can also occur, such as a feeling of agitation and in some cases sadness. See also the Pharmacotherapeutic compass.

The side effects generally occur mainly in the first week, but depending on the sensitivity of the patient, they can also last a little longer. Rarely have we seen any serious mental side effects so far. However, it may be that the 'normal side effects' sometimes occur to a greater extent and last for a longer period of time than in people who do not have PCS.

Important: if the patient has previously shown to be highly sensitive to medication in general (or to related medications), it is possible to have a pharmacogenetic test done. Occasionally, patients have a deficiency of certain enzymes to properly break down this medication.
Important: 1st generation anti-depressants should preferably not be combined with 2nd generation anti-depressants (e.g. do not combine amitriptyline, mirtazapine, etc. with an SSRI) with the possible risk of a serotonergic syndrome. However, in lower doses and with the SSRIs mentioned above, it is usually not a problem.

Important information regarding building up medication and possible side effects
If the PCS patient experiences almost no effect at the starting dose or after 1 or 2 increases, a further increase is certainly useful (depending, of course, on any side effects). If after another increase in dosage no change after 6-8 weeks is noticeable, there is little chance that this SSRI medication will show any effect. A switch can certainly be considered (see below under 'Switching').

Important: If side effects have persisted for 3 weeks during the start of the SSRI medication and have not diminished, the patient is most likely too far above the effective dose; a step back is then appropriate. If in some cases the side effects are too disruptive, it is important to reduce the dosage sooner. It is then important to monitor whether the side effects have decreased sufficiently and whether the patient still experiences an effect at this minimum dose. This may be supported with a nutritional supplement (see below). It is advisable to request a **pharmacogenetic test** so that it can be determined whether a possible switch is useful.

If, after an initial improvement with the starting dose, a relapse follows after increasing the dosage (a relapse that is the result of side effects), it is important to go back to the starting dose (or the last dose at which everything went well) and remain on this dose for a few weeks. It may be the case, especially in the case of hypersensitivity to medication, that the starting dose is enough.

If the side effects generally persist for more than a week (following an increase in the dosage) and do not decrease or are seriously disruptive to the patient, it can be assumed that this dosage is too high and the dosage must be reduced. In that case, the SSRI medication in question may not be broken down properly, causing accumulation. If the patient notices that the side effects at the lower dose are significantly reduced and a

positive effect is also experienced, this dose can be considered the best achievable. However, if the side effects linger on it's best to reduce the dosage further, request a pharmacogenetic test, switch to another SSRI and/or try starting nutritional supplements (see below). Drops are also possible with Citalopram and Escitalopram, so that the dose can be increased in smaller steps.
Important: it must be emphasized that the dosage of activity and energy deserves continued attention, even in addition to SSRI medication. An increased mental energy level can be a pitfall for increasing physical activity too quickly. It is therefore important to carefully phase in 'doing more' (1 activity, extension or intensification at a time, and only expand if this goes well for a few days). Because the physical energy supply is still vulnerable, exhaustion and relapse are otherwise possible.

Supportive nutritional supplements
In practice, it appears that NAC/Fluimucil can help to reduce overstimulation in addition to SSRI medication. NAC stands for N-Acetyl-L-Cysteine. To have an effect, it must be taken for a longer period of time in a dosage of 600 mg three times a day. This can be done in addition to taking SSRI medication. See below for points of interest. It forms the antioxidant glutathione and stimulates the executive cells (glutaminergic cells) in places that are important for concentration and planning. It therefore ensures a better selection of stimuli and thus supports the effect of SSRI medication. Effects of NAC can also manifest themselves in a (further) decrease in an (unusually) increased heart rate and headache complaints.
Resveratrol (100 mg twice a day) can also be of good use. It is an antagonist of a certain receptor of the kynurine pathway and thus inhibits this pathway in favor of the serotonin pathway. In terms of effect, it is similar to the anti-cancer drug that was referred to by immunologist Lutter (august 2023) but is not yet on the market. 5-HTP (2 x 50 mg), used in combination with SSRI medication also ensures that tryptophan is used safely for the production of serotonin. For supporting information, see:

- https://www.sciencedirect.com/science/article/pii/S1876034122003021
- https://www.sciencedirect.com/science/article/pii/S075333222200155X
- https://www.cell.com/cell/pdf/S0092-8674(23)01034-6.pdf

Supportive medication
PCS patients may have histamine hypersensitivity, which can also cause complaints such as poor sleep, muscle pain, dizziness, fatigue, nausea, sweating, sore throat, etc. Trying an antihistamine is therefore recommended and can be combined with SSRI medication. A low-histamine diet can support this. If you have poor sleep, a sedating antihistamine can be considered, such as a prescription of promethazine, 5 to 30 mg. This has a sleep-inducing effect (start at the starting dose). Promethazine is an H1 inhibitor and may also enhance the effect of an SSRI. An H1 inhibitor is also available at the drugstore as, for example, cetirizine.

Vitamin B12 and D

A vitamin B12 or D deficiency is quite common in PCS patients. It is recommended to have these vitamins determined and to supplement any identified deficiencies because a deficiency may possibly worsen the symptoms of PCS. Vitamin D may also have an important preventive function in reducing the risks of a serious disease progression in case of reinfection. See an important meta-analysis of RCTs in Clinical Nutrition, Sept. 2023.

Sensitivity to SSRI medications

If the patient is or appears to be very sensitive, half a starting dose can also be used. It is also advisable to do the build-up at a slower pace and spread it out over a longer period of time. See also the text above regarding dosage adjustment and requesting a pharmacogenetic test.

Switch

A switch can be made if the patient experiences many side effects from a particular drug and wants to switch to a (different) SSRI. Instead of using the switch table, the 'switch' can also take place in such a way that the PCS patient suffers as little as possible from 'tapering' side effects. This is in principle possible by skipping the old SSRI for 1 day and starting the next day with the starting dose of the new SSRI, staying on this dose for a number of days to 1 week and then immediately (if applicable) building up to the intended dose. *For advice and consultation, especially if you are sensitive to medication changes, see the mentioned contact details.*

Important: if there are signs of confusion, fever, chills and/or cramps, a doctor should always be contacted in view of a possible serotonergic syndrome.

Tapering off medication

An SSRI is expressly intended to be temporary; it is about reducing the inflammatory reactions by influencing the sigma1 receptor (which prevents virus replication), inhibiting the overstimulation of the kynurenine pathway and, as it were, 'training' the brain to, among other things, restore balance to 'the hormonal axis'. The brain then has to learn to do it itself again. It is currently not possible to say with certainty how long this will be temporary. We use two years as a guideline now. The same as with a first depression. But depersonalization disorder sometimes requires treatment for 4 to 6 years, so we have to wait and see how long this is the case with PCS.

Important: do not reduce the dose earlier than after 1 (or 1.5) year, and in case of longer-standing complaints, after 2 years. An SSRI is not addictive, but the brain must gradually take over its task again, which is why the reduction must be done in small steps. We recommend using tapering medication during the reduction so that the PCS patient has to suffer as few side effects as possible.

This can be further agreed in consultation with the pharmacy. 'Tapering strips', in which the dosage is tailor-made phased out, are helpful in this regard. We recommend following the guidelines regarding 'Discontinuation of SSRIs and SRNIs', where pace and dosage steps are described in the presence and absence of additional risk factors.

The patient can also temporarily take 5-HTP during the phasing out (research shows that serotonin levels drop during phasing out - this is part of the problem that makes phasing out difficult for some). For this purpose, 50 mg 5-HTP can be taken up to twice a day. It is important to look carefully at the actual content of the active substance in capsules.

The importance of guarding you limits

It is important to emphasize that it is wise to dose the energy properly and to monitor the limits during and after the use of an SSRI. A relapse is otherwise possible. Sufficient attention to relaxation is also important.

Literature

Intervention study SSRI treatment in PCS patients

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Previously published on early treatment of COVID-19 with Fluvoxamine

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- Lee at al. (April 2022), *Fluvoxamine for Outpatient Management of COVID-19 to prevent hospitalization; a Systematic Review and Meta-Analysis*, JAMA, https://doi.org/10.1001/jamanetworkopen.2022.6269

Regarding helping to prevent Post Covid complaints

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Regarding the possible mechanisms of action in Post-Covid Syndrome

Regarding the association between serotonin and Post Covid complaints

- Wong et al. (Oct. 2023), Serotonin reduction in post-acute sequelae of viral infection, in Cell, https://doi.org/10.1016/j.cell.2023.09.013

- Guo, L. *et al.* Prolonged indoleamine 2,3-dioxygenase-2 activity and associated cellular stress in post-acute sequelae of SARS-CoV-2 infection. *EBioMedicine* **94**, 104729 (2023).
- Lim, C. K. *et al.* Kynurenine pathway metabolomics predicts and provides mechanistic insight into multiple sclerosis progression. *Sci Rep* **7**, 41473 (2017).
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Influence on hypothalamic-pituitary-adrenal axis

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- Handbook of Clinical Neurology, Vol. 106 (3rd series) Neurobiology of Psychiatric Disorders.T.E Schlaepfer and C.B. Nemeroff, Editors # 2012 Elsevier B.V. All rights reserved. Chapter 8 Neurotransmitters and neuropeptides in depression A.-M. BAO 1, 2 *, H.G. RUHE´ 3, S.-F. GAO 1, AND D.F. SWAAB 21 Department of

  Neurobiology, Institute of Neuroscience, Zhejiang University School of Medicine, Hangzhou, China 2 Netherlands Institute for Neuroscience, Amsterdam, The Netherlands 3Program for Mood Disorders AMC/De Meren, Academic Medical Centre, University of Amsterdam
- https://scholarlypublications.universiteitleiden.nl/access/item%3A2898055/view

Immunological

- *Fluvoxamine and long COVID-19; a new role for sigma-1 receptor (S1R) agonists* | Molecular Psychiatry: https://www.nature.com/articles/s41380-022-01545-3 https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/sigma-1-opiate-receptor
- Staedtke et al. (2018): *Disruption of a self-amplifying catecholamine loop reduces cytokine release syndrome,* Nature, https://doi.org/10.1038/s41586-018-0774-y
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More energy due to a positive influence on the mitochondria

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Influence on the autonomic nervous system

- Zie literatuur bij *Invloed op hypothalamus-hypofyse-bijnier-as*

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