Do Selective Serotonin Reuptake Inhibitors (SSRIs) Promote Stroke Recovery within the First Year After Stroke? - A Cochrane Review

Summary with Commentary

Thomas Platz

The aim of this commentary is to discuss in a rehabilitation perspective the Cochrane Review “Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery” produced by Legg LA, Tilney R, Hsieh CF, Wu S, Lundström E, Rudberg AS, Kutlubaev MA, Dennis M, Soleimani B, Barugh A, Hackett ML, Hankey GJ, Mead GE; 2019. https://doi.org/10.1002/14651858.CD009

Background

Despite major achievements in both acute stroke care and rehabilitation, stroke is still the third leading cause of disability and years lived with stroke-related disability are increasing in societies worldwide. Although multi-professional specialized stroke care including rehabilitative treatment has been shown to reduce disability, that is, health-related limitations in activities of daily living and restrictions in participation in societal activities, and hence to promote independence after stroke, there is great interest in potential additional therapeutic options to promote recovery after stroke. One of these options are drugs that influence cerebral neurotransmitter levels and promote neuroplastic changes associated with functional recovery. Selective serotonin reuptake inhibitors (SSRIs) are a class of drugs that are widely used to treat mood disorders (depression, anxiety) and had been shown to have a potential to promote recovery after stroke in a first Cochrane Review on the subject in 2012. Meanwhile, more substantial clinical trial evidence became available warranting an update of the Cochrane Review.

Selective Serotonin Reuptake Inhibitors (SSRIS) For Stroke Recovery

Legg LA, Tilney R, Hsieh CF, Wu S, Lundström E, Rudberg AS, Kutlubaev MA, Dennis M, Soleimani B, Barugh A, Hackett ML, Hankey GJ, Mead GE; 2019. https://doi.org/10.1002/14651858.CD009

What Was the Aim of This Cochrane Review?

The aim of this Cochrane Review was to determine whether SSRIs promote recovery in people within the first
year post stroke and whether the treatment is associated with side effects.

**What Was Studied in the Cochrane Review?**

The population addressed in this review was stroke survivors within 12 months post stroke. The interventions studied were SSRIs including fluvoxamine, fluoxetine, sertraline, citalopram, and paroxetine administered at any dose, duration, and delivery mode for any reason. The SSRI intervention was compared to placebo treatment or usual care. The outcomes studied were disability as measured mostly using Barthel index (BI) or Functional Independence Measure (FIM) or other tools and independence as measured using the modified Rankin Scale (primary outcomes) as well as neurological impairments, depression, anxiety, quality of life, fatigue, healthcare cost, death, adverse events, and leaving the trial early (secondary outcomes).

**Search Methodology and Up-to-Dateness of the Cochrane Review?**

The review authors extensively searched for studies that had been published up to July 2018.

**What Are the Main Results of the Cochrane Review?**

Overall, the review included 63 randomized controlled trials (RCTs) recruiting 9168 participants, of whom 32 were using fluoxetine, 11 using paroxetine, 8 using sertraline, 8 using citalopram, 2 using escitalopram, and 1 using either fluoxetine or sertraline.

Of those, only 3 RCTs (all using fluoxetine) were at low risk of bias for all of the assessed domains. The meta-analyses were primarily based on these three placebo-controlled RCTs and indicated:

- no effect of SSRIs compared to placebo on disability scores: standardized mean difference (SMD) −0.01 (95% confidence interval [CI], −0.09 to 0.06; 2 studies, 2829 participants) or independence: relative risk (RR) 1.00 (95% CI 0.91 to 1.09; 3 studies, 3249 participants); (both moderate-quality evidence);
- SSRIs did not improve neurological deficit scores: SMD −0.3 (95% CI, −0.63 to 0.04; 2 trials, 142 participants; moderate-quality evidence);
- whereas SSRIs reduced the average depression scores slightly: SMD -0.11 (95% CI, -0.19 to -0.04; 2 trials, 2861 participants; moderate-quality evidence);
- and increased the number of gastrointestinal side effects: RR 2.19 (95% CI, 1.00 to 4.76; 2 studies, 148 participants; moderate-quality evidence);
- treatment with SSRIs was not associated with a higher number of seizures: RR 1.47 (95% CI, 0.99 to 2.18; 3 studies, 3275 participants; moderate-quality evidence);
- nor with a higher death rate: RR 0.99 (95% CI, 0.79 to 1.25; 3 studies, 3254 participants; high-quality evidence);
- for other secondary outcomes, that is, motor deficits, quality of life, fatigue, and leaving the study early, no differential effects of SSRI were documented; healthcare costs had not been investigated in the trials included.

When all studies (regardless of risk of bias) were used for a sensitivity analysis, SSRIs improved disability scores slightly compared to placebo or standard care/practice: SMD 0.23 (95% CI, 0.18 to 0.29; P < .001; 26 studies, 5334 participants) with considerable heterogeneity between trials (I² = 92%).

**How Did the Authors Conclude?**

The authors concluded that they found no reliable evidence regarding routine use of the SSRIs to promote recovery after stroke based on the meta-analyses of three trials at low risk of bias, which indicated lack of improvement in recovery from stroke with SSRIs. They identified potential improvements in disability when trials at high risk of bias were included in the analyses and hence a high risk to overestimate beneficial effects.

**What Are the Implications of the Cochrane Evidence for Practice in Rehabilitation?**

The strength of this Cochrane Review is that its primary analyses were based on data from trials at low risk of bias with a substantial number of participants providing a valid, clinically speaking clear estimate of no therapeutic effect on disability indicating that SSRIs prescribed for stroke survivors within the first year after stroke did not reduce disability or dependence.

The results of the meta-analyses have largely been driven by a single large trial; accordingly, future evidence from other large trials using SSRIs with different approaches (e.g., specific drug and dosage used, time post stroke, duration of treatment, combination with training etc.) might modify “the overall picture.”

A slight clinical benefit could be corroborated for depression but not for other aspects of interest.

The SSRI treatment was found to be acceptable to patients (no increase in the number of participants leaving the study early), and the results of the adverse event analyses were not worrisome (increased gastrointestinal side effects with SSRI prescription as expected, no increase in seizures or death rates).

In conclusion, the overall benefit-risk analysis speaks against the routine use of SSRIs as an adjunct treatment and means to reduce disability and dependence among stroke survivors within the first year after stroke.

**Acknowledgments**

The author thanks Cochrane Rehabilitation and Cochrane Stroke Group for reviewing the contents of the
Cochrane Corner. This work was supported by the BDH Bundesverband Rehabilitation e.V. (charity for neuro-disabilities) by a nonrestricted personal grant to TP. The sponsors had no role in the decision to publish or any content of the publication.

References

1. Legg LA, Tilney R, Hsieh CF, et al. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. *Cochrane Database Syst Rev*. 2019;11:CD009286. https://doi.org/10.1002/14651858.CD009286.pub3.

2. Johnson W, Onuma O, Owolabi M, Sachdev S. Stroke: a global response is needed. *Bull World Health Organ*. 2016;94:634-634A.

3. GBD 2015. Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the global burden of disease study 2015. *Lancet*. 2016;388:1545-1602.

4. Stroke Unit Trialists’ Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev*. 2013;9:CD000197.

5. Mead GE, Hsieh CF, Lee R, et al. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. *Cochrane Database Syst Rev*. 2012;11:CD009286.

Disclosure

T.P. Center for Neurorehabilitation, Ventilation and Intensive Care, Spinal Cord Injury Unit, BDH-Klinik, Greifswald, Germany; and Neurorehabilitation Research Group, University Medical Center Greifswald, Greifswald, Germany. Address for correspondence: T.P.; e-mail: t.platz@bdh-klinik-greifswald.de

Disclosure: The author declares no conflicts of interest.

Submitted for publication April 24, 2020; accepted April 27, 2020.