View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Göteborgs universitets publikationer - e-publicering och...

Göteborg, 2019

On the Effects of Serotonin Reuptake Inhibitors in Major Depression

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hörsal Arvid Carlsson, Medicinaregatan 3, fredagen den 15 februari, klockan 13:00

av Fredrik Hieronymus

Fakultetsopponent: Prof. Stuart Montgomery,
Imperial College London, United Kingdom

Avhandlingen baseras på följande delarbeten

I. **Fredrik Hieronymus**, Johan F. Emilsson, Staffan Nilsson, Elias Eriksson. *Consistent superiority of selective serotonin reuptake inhibitors over placebo in reducing depressed mood in patients with major depression*. Mol. Psychiatry 2016;21:523-530.

II. **Fredrik Hieronymus**, Staffan Nilsson, Elias Eriksson. *A mega-analysis of fixed-dose trials reveals dose-dependency and a rapid onset of action for the antidepressant effect of three selective serotonin reuptake inhibitors*. Transl. Psychiatry. 2016;6:e834.

III. **Fredrik Hieronymus**, Alexander Lisinski, Staffan Nilsson, Elias Eriksson. *Efficacy of selective serotonin reuptake inhibitors in the absence of side effects: a mega-analysis of citalopram and paroxetine in adult depression*. Mol. Psychiatry. 2018;23:1731-1736.

IV. Jakob Näslund, **Fredrik Hieronymus**, Alexander Lisinski, Staffan Nilsson, Elias Eriksson. *Effects of selective serotonin reuptake inhibitors on rating-scale-assessed suicidality in adults with depression.* Br. J. Psychiatry 2018;212:148-154.

V. **Fredrik Hieronymus**, Alexander Lisinski, Staffan Nilsson, Elias Eriksson. *Impact of baseline severity on the effects of selective serotonin reuptake inhibitors in depression: an item-based patient-level post hoc analysis*. Submitted.

VI. Alexander Lisinski, **Fredrik Hieronymus**, Jakob Näslund, Staffan Nilsson, Elias Eriksson. *Item-based analysis of the effects of duloxetine in depression: a patient-level post hoc study*. Submitted.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

GÖTEBORGS UNIVERSITET

Göteborg, 2019

On the Effects of Serotonin Reuptake Inhibitors in Major Depression

Fredrik Hieronymus

Department of Pharmacology, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Abstract

This thesis focuses on the antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) and how these are reflected by the Hamilton Depression Rating Scale (HDRS). To this end, we have assembled a large data set of placebo-controlled SSRI trials in major depression, and used this for a series of post-hoc patient-level analyses.

Thus, in a population of 8 262 patients treated with either of four SSRIs (citalopram, fluoxetine, paroxetine, or sertraline) or placebo, we have assessed (1) to what extent the various symptoms included in the HDRS separate between active treatment and placebo, and contrasted this to the sum-score of all HDRS items, which has been the conventional effect parameter, (2) whether the effects of SSRIs are dose-dependent, (3) whether side effects are necessary for SSRIs to outperform placebo, (4) if SSRIs increase or decrease suicidal ideation, and (5) whether only patients with high baseline depression severity respond to treatment with SSRIs.

We found that the influence of drug treatment on individual HDRS items differs vastly with regard to both the size and direction of effect. While depressed mood and other core symptoms of depression are consistently improved by SSRI treatment, HDRS items that may reflect typical SSRI side effects, such as e.g., gastrointestinal symptoms and sexual symptoms, respond, on average, negatively. The HDRS sum-score thus represents an aggregate of beneficial effects on core depression symptoms and detrimental effects on possible side-effect related items. Further, we suggest that the balance between these domains vary with time under treatment, with side-effects being relatively more influential early in treatment, thereby obfuscating significant positive effects otherwise evident as early as after one week of treatment.

We also found evidence for a dose-response relationship, i.e., very low SSRI doses were more effective than placebo, but less effective than higher doses; this relation plateaued at the low to mid-range of currently recommended doses. We did not find any evidence in support of the hypothesis that side effects be an indispensable prerequisite for antidepressant efficacy, or that side effect severity moderates response. We could replicate previous studies showing SSRIs to decrease suicidal ideation in subjects ≥ 25 years of age, but could not detect a significant influence of SSRIs in either direction in young adults ($18 \leq \text{age} < 25$). We found baseline symptom severity to be positively associated with SSRI efficacy when measured by the HDRS sum-score. This was however not the case for core depression symptoms where instead patients improved equally regardless of baseline severity. We suggest this to be partly due to non-core symptoms being absent in low-severity patients, thus leaving less room for improvement and more room for worsening on side-effect related items. Most of these observations were replicated in a population of 3575 patients from studies of the serotonin and noradrenaline reuptake inhibitor duloxetine.

We conclude i) that the sum-score of the HDRS rating scale is an insufficient and insensitive measure of antidepressant efficacy, ii) that the use of this outcome parameter has led to an underestimation of the true efficacy of SSRIs and SNRIs, particularly at the early phase of treatment and in subjects with relatively mild depression, iii) that normal doses of antidepressants are superior to low doses but not inferior to high doses, iv) that antidepressant effects are not, as has been suggested, secondary to side effects breaking the blind, and v) that the net effect of antidepressants on suicidality is beneficial, at least in subjects ≥ 25 years of age. In conjunction, the results rebut many of the claims that have been put forward by those questioning the usefulness of antidepressants.

Keywords: antidepressants, antidepressive agents, depression, major depressive disorder, selective serotonin reuptake inhibitor, SNRI, SSRI.

ISBN: 978-91-7833-312-7 (TRYCK) http://hdl.handle.net/2077/58234
ISBN: 978-91-7833-313-4 (PDF)