On the Effects of Serotonin Reuptake Inhibitors in Major Depression

Akademisk avhandling

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

Avhandlingen baseras på följande delarbeten


On the Effects of Serotonin Reuptake Inhibitors in Major Depression

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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 ≤ 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.