Review: little evidence to support dose escalation of selective serotonin reuptake inhibitors in non-responders

Ruhé HG, Huyser J, Swinkels JA, *et al*. Dose escalation for insufficient response to standard-dose selective serotonin reuptake inhibitors in major depressive disorder: systematic review. *Br J Psychiatry* 2006;**189**:309–16.

Q Is dose escalation of selective serotonin reuptake inhibitors effective for treating major depressive disorders in people who do not respond to standard doses?

METHODS

Design: Systematic review.

Data sources: MEDLINE, EMBASE, CINAHL, and PsycINFO (search date February 2005).

Study selection and analysis: Included studies were randomised controlled trials (RCTs) or meta-analyses based on systematic reviews assessing the effects of dose escalation of selective serotonin reuptake inhibitors (SSRIs) for major depressive disorders not responding to standard SSRI doses. Studies were screened independently by two reviewers. Included studies were critically appraised, assigned a level of evidence, and data extracted using standardised forms and criteria. No meta-analysis was conducted due to heterogeneity of the timing of dose escalation.

Outcomes: Response (defined as ⩾50% reduction in Hamilton Rating Scale for Depression (HRSD) score or Clinical Global Impression (CGI) improvement or severity score ⩽2); remission (defined in studies as HRSD score ⩽7 or ⩽8).

MAIN RESULTS

Eleven studies met inclusion criteria (8 primary studies and 3 systematic reviews). The 3 systematic reviews had methodological weaknesses, including meta-analysis of heterogeneous studies. Results from 4 lower quality RCTs suggested that dose escalation before 4 weeks of treatment with the standard dose had no effect on response or remission. One good quality RCT found that dose-escalation after 6 weeks of treatment was less effective than continuing with the standard dose alone. Two lower quality RCTs provided limited evidence that dose escalation of fluoxetine after 8 weeks' treatment may increase response compared with adding lithium or desipramine, although it was not clear if this increase was significant in both studies. Increasing doses were associated with higher study withdrawals in all included studies; this was related to increased side effects in some studies.

CONCLUSIONS

There is little evidence to support dose-escalation of SSRIs for improving depression in people who do not respond to standard doses. The available evidence is mostly of poor quality.

NOTES

One of the eight primary studies identified appeared to be an uncontrolled study. It is not clear why this study was included, and its results are not described above. The weaknesses of some of the RCTs were the inclusion of people with minor depression, absence of placebo controls, lack of power to detect clinically relevant differences, inadequate reporting of data and inadequate reporting of blinding.

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Commentary

In their systematic review, Ruhé and colleagues report on the current literature on dose escalation for insufficient response to standard-dose selective serotonin reuptake inhibitors (SSRIs) in major depressive disorder. Eight dose escalation studies and three meta-analyses were identified. The authors found limited evidence for superior efficacy of dose escalation over dose maintenance only after 8 weeks of preceding non-response had elapsed before randomisation. Earlier dose increases after 4 or 6 weeks did not benefit the patient. Adequate methods were applied for the systematic review and the authors' decision not to pool the results of the different studies in a meta-analysis appears appropriate due to significant heterogeneity of study designs.

Limitations of the identified studies addressed in detail by the authors were varying methodological quality, under-reporting of dropouts as well as dose increment schedules and different timing in dose escalation. Another potential source of bias is that patients randomised to dose escalation might discontinue the study due to side effects earlier than patients in the placebo group; their higher severity scores are reflected in the LOCF analysis, the most commonly applied statistical approach. The named limitations all sum up the methodological problems of three meta-analyses[1–3] (which did also not find a clear efficacy of dose increase) identified by the authors.

In the face of the review, the lack of evidence becomes apparent regarding what psychiatrists should recommend to patients who do not, or only partially, respond to treatment with SSRIs for 4–8 weeks. Current treatment guidelines[4] do name dose increase as an option but at the same time stress the low evidence level for this recommendation. Nevertheless an early dose increase after 4 weeks without clinical amelioration may be overhasty in the context of the current findings.

Based on the outcome of the current review, future studies should conduct randomisation after 8 weeks of insufficient treatment, a time point corroborated by data from Quitkin and colleagues[5] finding an earlier switch to be premature. Furthermore they should report on dose tolerant patients in addition to LOCF data and collect information on SSRI-plasma levels, which may help identify additional prognostic factors for response.

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1 Baker CB, Tweedie R, Duval S, *et al*. Evidence that the SSRI dose-response in treating major depression should be reassessed: a meta-analysis. *Depress Anxiety* 2003;**17**:1–9.
2 Bollini P, Pampallona S, Tibaldi G, *et al*. Effectiveness of antidepressants. Meta-analysis of dose-effect relationship in randomised clinical trials. *Br J Psychiatry* 1999;**174**:297–303.
3 Corruble E, Guelfi JD. Does increasing dose improve efficacy in patients with poor antidepressant response? A review. *Acta Psychiatr Scand* 2000;**101**:343–8.
4 NICE. *Depression: management of depression in primary and secondary care*. Clinical guideline 23. London: National Institute for Health and Clinical Excellence, 2004.
5 Quitkin FM, Petkova E, McGrath PJ, *et al*. When should a trial of fluoxetine for major depression be declared failed? *Am J Psychiatry* 2003;**160**:734–40.