Review: multiple daily doses of antidepressants are not more effective than single daily doses

Yildiz A, Sachs GS. ***Administration of antidepressants. Single versus split dosing: a meta-analysis.*** *J Affect Disord 2001 Oct;**66**:199–206.*

QUESTIONS: In patients with depression, are multiple daily doses (MDD) of antidepressants more effective than single daily doses (SDD)? Does the pharmacokinetic half life of a drug influence the antidepressant activity of single daily doses?

Data sources

Studies were identified by searching {PubMed}* with the terms antidepressants, single daily dosing versus, multiple daily dosing, and antidepressant efficacy.

Study selection

Studies were selected if they were randomised controlled trials (RCTs) that compared dosing schedules of the same antidepressant (with 1 group receiving SDD) and if the total daily dose in the SDD and MDD groups were the same.

Data extraction

Data were extracted on study characteristics, drug regimen, sample size, compliance, mean baseline rating on depression scales, and percentage change at end point. Treatment effects were calculated and weighted in a meta-analysis. 3 different weights were used for each treatment effect to reflect 3 different assumptions about the correlation between baseline and follow up depression scores (ρ=0.9 [worst case scenario], ρ=0.5, and ρ=0).

Main results

22 studies met the selection criteria, and 17 provided sufficient data for meta-analysis. Sample sizes ranged from 6–241 patients (mean 78 patients). Antidepressants were trazodone (5 RCTs), amitriptyline (3 RCTs), venlafaxine (1 RCT), nomifensine (1 RCT), bupropion (1 RCT), nefazodone (1 RCT), amoxapine (1 RCT), moclobemide (1 RCT), zimelidine (1 RCT), fluvoxamine (1 RCT), desipramine (1 RCT), doxepin (1 RCT), imipramine (1 RCT), clomipramine (2 RCTs), and mianserin (1 RCT). SDD and MDD did not differ in treatment effect. 10 studies of antidepressants with short half lives (< 12 h) did not show a difference in treatment effect between SDD and MDD (mean improvement from baseline 61% for SDD and 62% for MDD). In 3 studies of antidepressants with intermediate half lives (> 12 to < 24 h), SDD was better than MDD for all 3 treatment effects ($p < 0.001$ for worst case scenario [ρ=0.9]); the mean improvement was 58% for SDD and 51% for MDD. In 4 studies of antidepressants with long half lives (> 24 h), the difference in favour of SDD was statistically significant only when the correlation between baseline and follow up scores was assumed to be 0.9 (worst case scenario, p=0.01). The mean improvement from baseline was 90% for SDD and 87% for MDD.

Conclusions

In patients with depression, multiple daily doses of antidepressants are not more effective than single daily doses. Grouping the studies by pharmacokinetic half life of the drug does not show an advantage for multiple daily doses over single daily doses.

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For correspondence: Dr A Yildiz, Dokuz Eylul Medical School, Izmir, Turkey and Harvard Medical School, Boston, MA, USA
Agul_yildiz@hotmail.com

COMMENTARY

Single daily doses of antidepressants have always been considered inappropriate for short elimination half life drugs. The systematic review by Yildiz and Sachs, which stratified medications according to the pharmacokinetic half life of the drug, showed no difference in the extent of clinical improvement between SDD and MDD for short, intermediate, and long half life agents. This lack of differences suggests that sustained therapeutic serum concentrations are not necessary for achievement of therapeutic activity. Although this review reported the proportion of completers of the corresponding studies, the efficacy analysis, based on the comparison of the improvement on the Hamilton score, has inevitably excluded those patients who did not complete the study. This exclusion leaves uncertainty about the effectiveness of SDD compared with MDD in clinical practice, a crucial point in the evaluation of a strategy developed to improve tolerability.

No study found differences in adverse effects between SDD and MDD, suggesting that splitting the dose does not improve tolerability. Unfortunately, data on adverse effects were not sufficient for meta-analysis of the trials, and individual studies had insufficient power to detect differences. Moreover, no comparison of the overall dropout rate between SDD and MDD was done. However, looking at the proportion of completers, it seems unlikely that the SDD strategy is less tolerable than the MDD one. Information on the overall dropout rate between SDD and MDD is needed to estimate the tolerability of the 2 dosing schedules.

Dropout rates represent only a rough measure of adverse effects; patients discontinue the study for many reasons, including adverse effects, inefficacy, treatment complexity, and protocol violations; dropout rates may therefore be considered an indicator of the overall treatment acceptability. The question of whether SDD is associated with fewer or more dropouts than MDD remains a key issue. One can speculate that MDD, by reducing adverse reactions, is associated with fewer dropouts, or exactly the contrary, that SDD, by increasing treatment simplicity, is associated with fewer dropouts. In any case, if included in the calculation of treatment response, dropouts would likely have some effect on the estimate of effectiveness.

In future, clinical trials will clarify whether SDD or MDD should be adopted in practice. In the meantime, clinicians should systematically follow cohorts of typical patients receiving SDD and MDD to generate information on the probability of different outcomes (recovery, adverse reactions, and dropouts), and on variables (SDD *v* MDD) associated with these outcomes.

Corrado Barbui, MD
University of Verona
Verona, Italy

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