EDITORIAL

What is the optimal antidepressant dose?

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THE OPTIMAL DOSE OF A SECOND-GENERATION ANTIDEPRESSANT LIES TOWARDS THE LOWER END of its licensed dose range, a systematic review and dose-response meta-analysis has found.[1]

Data were obtained from a comprehensive 2016 network meta-analysis. Double blind randomised controlled trials were included if they compared one antidepressant with another or placebo in the treatment of major depression in adults without a serious concomitant physical illness.

Primary outcomes were treatment response (≥ 50% reduction in depression severity), tolerability (dropouts due to adverse effects) and acceptability (all-cause dropouts) after 8 weeks of treatment (range 4-12 weeks).

Five SSRIs (citalopram, escitalopram, fluoxetine, paroxetine and sertraline) were analysed together with mirtazapine and venlafaxine. The SSRIs were analysed as a group after converting drug doses to equivalent fluoxetine doses. Dose-outcome relationships were plotted for each of the three primary outcomes.

There were 77 studies with a total of 19,364 participants (mean age 42.5, 61% female) included in the review. For SSRIs, the dose-response curve showed a gradual increase in the probability of response up to a fluoxetine-equivalent dose of between 20 mg and 40 mg. For higher doses in the range 41-80 mg the graph showed a plateau or slight decrease in response probability. However, the adverse effects dropout rate continued to increase steeply throughout the dose range. The U-shaped dose-acceptability curve indicated an optimal dose between 20 mg and 40 mg.

The dose-response curve for venlafaxine showed a fairly steep rise in the probability of response up to a dose of 75-150 mg followed by a more gradual rise for doses in the range 151-375 mg. The curve for mirtazapine showed an increase in response probability up to a dose of 30 mg followed by a decline with doses in the range 31-60 mg. For both drugs the adverse effects dropout rate increased steeply with increasing dose and the optimal dose was towards the lower end of the licensed dose range.

Thus the optimal dose range for fluoxetine is 20-40 mg. Increasing the dose above 40 mg is unlikely to provide any additional therapeutic benefit and will increase the risk of adverse effects. The equivalent optimal dose ranges for the other SSRIs (rounded up or down to the nearest 10 mg) are: citalopram 20-40 mg, escitalopram 10-20 mg, paroxetine 20-30 mg and sertraline 50-100 mg. The optimal dose of mirtazapine is 30 mg: increasing the dose above 30 mg will reduce both efficacy and tolerability. For venlafaxine a dose range of 75-150 mg is considered optimal.

The authors caution that the optimal doses for older patients (age ≥ 65) or those with comorbid physical conditions may be lower. Of necessity, the studies used a fixed-dose regimen which may have led to higher dropout rates than would occur in clinical practice where side effects can be mitigated by slower dose titration.[2]

> **'The lower range of the licensed dose will probably achieve the optimal balance between efficacy, tolerability and acceptability'**

NICE recommends that, where there has been no, or minimal, response to a therapeutic dose of an antidepressant after 3-4 weeks, practitioners should consider either:

1 Increasing the dose in line with licensed dose ranges, providing there are no significant side effects, or
2 Switching to another antidepressant. If there is some improvement by 4 weeks, treatment should be continued for a further 2-4 weeks; at that point, if the response is still not adequate, consideration should be given to changing to an alternative antidepressant.[3]

In contrast, the American Psychiatric Association recommends that, for those who have partially responded to initial treatment, 'doses of antidepressants should be maximised, side effects permitting, before changing to a different antidepressant medication.'[4]

The review authors conclude that: 'for the majority of patients receiving an SSRI, venlafaxine, or mirtazapine for the acute-phase treatment of their major depressive episode, the lower range of the licensed dose will probably achieve the optimal balance between efficacy, tolerability, and acceptability. Clinical guidelines need to incorporate these findings.'

REFERENCES
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