Mental health

Predicting which older patients will fail to respond to antidepressants

Older people with higher levels of depression severity are unlikely to respond to first-line antidepressant treatment, particularly if they have chronic depression, guilt or marked functional impairment, a US open label study has found.

A total of 453 participants were recruited in a secondary care setting and completed the study. Eligible patients were aged 60 or above with current non-psychotic unipolar major depression.

The Montgomery-Asperg Depression Rating Scale (MADRS) was used to determine baseline depression severity and to monitor response to treatment. The 17-item Hamilton Rating Scale for Depression was used to assess additional baseline symptoms such as guilt which do not appear in the MADRS.

Participants were treated with venlafaxine, started at 37.5 mg daily and titrated to an initial target dose of 150 mg daily. After six weeks, nonremitters (MADRS score > 10) had further dose titration to a target dose of 300 mg daily.

Participants were followed up after one week, two weeks and then two-weekly to the end of the three-month study period. At each visit a form of case management was provided and the MADRS was administered. There was no formal psychotherapy.

A statistical technique, group-based trajectory modelling, was used to divide the cohort into six subgroups with distinct trajectories of treatment response over time. Three of the subgroups (with low, moderate and high baseline severity) clearly responded to treatment. Of the other three subgroups, two with high baseline severity did not respond at all whereas a group with moderate baseline severity appeared to respond initially but the response then stalled.

Of the total cohort, 202 participants (45%) were classified as responders, but of those with high baseline depression severity only 25/188 (13%) were responsive.

After adjustment for demographic, lifestyle and health factors, a non-responsive trajectory was significantly associated with:

- High baseline severity
- Prolonged duration
- Less subjective sleep loss
- More guilt
- Greater work/activity impairment

However, the wide confidence intervals and failure to demonstrate significance in all nonresponse groups means that the results for duration, guilt and functional impairment should be treated with caution.

Good performance on a delayed memory word list recognition test was associated with having a rapid response, adjusted odds ratio 2.22 (95% CI: 1.18-4.20). However, the authors acknowledge that this test in isolation is not sufficient to identify or rule out mild cognitive impairment.

The optimum MADRS cut-off score separating severe from moderate depression is ≥ 31.[1] The three high severity subgroups had mean baseline scores which were either just above or just below this boundary, indicating moderate-severe depression.

The authors suggest that high severity alone may not be sufficient to predict nonresponse, but that patients with a combination of risk factors should be followed up more closely and considered for treatment augmentation.

In fact, both NICE[2] and the British Association for Psychopharmacology[3] already recommend that patients with severe depression should receive combination treatment with antidepressants and CBT. A recent study provided evidence that combination treatment does improve outcomes in patients with severe nonchronic depression, but not for those with an episode duration of two years or more.[4]

A practical difficulty in depression management is deciding how long to persist with first-line treatment before concluding that it is ineffective. NICE recommends treatment adjustment if there is absent or minimal response after three to four weeks.

If there is partial improvement, NICE recommends that treatment should be continued for a further two to four weeks at which point a change of treatment should be considered if the response is still not adequate.[2]

However, elderly patients may be slower to respond to treatment and a small but significant minority of patients are late responders.[3]

The graph of response trajectories in the present study shows that for those with more severe depression, clear separation between responders and nonresponders does not occur until the completion of eight weeks' treatment.

For older patients with moderate-severe depression, I would suggest that we:

- Offer combination treatment with CBT particularly to those with higher levels of guilt or functional impairment
- Seek guidance from secondary care for those with chronic depression (two years or more)
- Do not conclude that antidepressant treatment is ineffective before eight weeks' treatment has been completed.

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● **Smagula SF, Butters MA, Anderson SJ et al. Antidepressant response trajectories and associated clinical prognostic factors among older adults. *JAMA Psychiatry* 2015;doi:10.1001**

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