

The combination of nefazodone and psychotherapy was more effective than either treatment alone in chronic depression

Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med* 2000 May 18;342:1462-70.

QUESTION: In patients with chronic forms of major depression, how effective is nefazodone, psychotherapy, and their combination in reducing relapse?

Design

Randomised (allocation concealed*), blinded (outcome assessor)*, controlled trial with 12 weeks of follow up.

Setting

12 academic centres in the US.

Patients

681 patients between 18 and 75 years of age (mean age 43 y, 65% women) with a *DSM-IV* diagnosis of a chronic major depressive disorder of at least 2 years duration and a score of at least 20 on the 24 item Hamilton Rating Scale for Depression (HRSD). Exclusion criteria included a history of seizures, severe head trauma, or stroke; high risk of suicide; history of psychotic symptoms or schizophrenia; bipolar disorder; eating disorder; obsessive compulsive disorder; dementia; antisocial, schizotypal, or severe borderline personality disorder; a principal diagnosis of panic, generalised anxiety, social phobia, or post-traumatic stress disorder; and substance abuse. 97% were included in the analysis.

Intervention

226 patients were assigned to nefazodone, initial dose 200 mg/day increased to 300 mg/day during the second week and increased at weekly increments of 100 mg/day to a maximum dose of 600 mg/day. 228 patients were assigned to the cognitive behavioural analysis system of psychotherapy with twice weekly sessions during weeks 1 through 4 and weekly sessions during weeks 5 through 12. 227 patients were assigned to a combination of both treatments.

Main outcome measures

Remission was defined as a score of 8 or less on the HRSD at weeks 10 and 12. For those who did not have remission, a satisfactory response was defined as a reduction in the HRSD by at least 50% from baseline and a score of 15 or less.

Main results

The overall rate of response (including both remission and satisfactory response) was 48% in both the nefazodone group and the psychotherapy group compared with 73% in the combined treatment group (table).

Conclusions

A combination of nefazodone and psychotherapy was more effective than either treatment alone in major chronic depression.

*See glossary.

Nefazodone or psychotherapy v combined treatment in major chronic depression at 12 weeks†

Outcome	Combined treatment	Nefazodone or psychotherapy	RBI (95% CI)	NNT (CI)
Remission or satisfactory response	73%	48%	53% (31 to 80)	4 (3 to 7)

†Abbreviations defined in glossary; RBI, NNT, and CI calculated from data in article.

COMMENTARY

Although both cognitive behavioural therapy (CBT) and antidepressants are effective in the treatment of depression, chronic depression does not respond as well to either treatment compared with acute depression. Chronic depression is associated with incomplete remission in approximately 20–30% of patients and with higher rates of relapse than for the acute form of the disorder.¹ Chronic depression is also associated with increased healthcare service use, impairment in functioning, and a poor response to monotherapies. These findings combine to suggest that chronic depression is a large public health problem and one of the biggest challenges facing researchers of depression today.

In their well designed, randomised, multicentre study, Keller *et al* found a distinct advantage for combined therapy over monotherapy. Rates of remission were higher among patients receiving a combination of nefazodone and the cognitive behavioural analysis system of psychotherapy. The results show that for every 4 patients treated with combined therapy, you would have 1 additional remission over a 12 week period compared with monotherapy.

The findings are striking, and the magnitude of the effect of combined treatment is impressive. The addition, however, of a placebo control group would have helped to clarify whether combining treatments has a truly additive effect. For example, in a recent multicentre study on panic disorder, investigators found that although medication plus CBT was superior to medication alone or CBT alone, the medication plus CBT group did not fare better than a pill placebo plus CBT group in the acute phase.² That said, it is often difficult to recruit patients for placebo studies in depression, and the authors appear to have increased sample size rather than limit the generalisability of the findings by including a placebo arm.

Finally, given the chronicity and higher rates of relapse seen in these patients, it will be important to watch for the results of maintenance and follow up studies that are currently in progress. Nevertheless, the study is well designed, the results are consistent with previous studies with smaller samples, and the findings suggest that combined medication and psychotherapy may be the short term treatment of choice for patients with chronic depression.

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- 1 Keller MB, Klerman GL, Lavori PW, *et al*. Long-term outcome of episodes of major depression. Clinical and public health significance. *JAMA* 1984;252:788–92.
- 2 Barlow DH, Gorman JM, Shear MK, *et al*. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomised controlled trial *JAMA* 2000;283:2529–36.