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Editorial

Prevention of first-episode depression: progress and potential

Robert G. Robinson and Ricardo E. Jorge

Summary
Preventive intervention for first-episode depression is an exciting, emerging field. Many questions remain, however. Should we target patients who have sub-syndromal symptom elevations (i.e. indicated intervention) or should we intervene in high-risk groups (i.e. selective intervention)? Furthermore, should primary outcomes be incident depressions or long-term decreases in morbidity or mortality?

Declaration of interest
None.

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Categorising preventive interventions

The Institute of Medicine Committee on Prevention of Mental Disorders recommended in 1994[1] that prevention in psychiatry should be referred to as 'preventive intervention', defined as an intervention before the patient receives a diagnosis. Preventive interventions, furthermore, were categorised as 'indicated' (i.e. treating high-risk individuals with premorbid signs or symptoms), 'selective' (i.e. treating individuals with demonstrated increased risk of developing illness) and 'universal' (i.e. treating whole populations including all levels of risk).

Prior preventive intervention studies

Although there is a large literature on the prevention of recurrent depression using maintenance therapy with either anti-depressants[2] or psychological treatments[3] or both, the only studies of prevention using participants with no prior history of mood disorder are recent selective intervention studies among high-risk populations with physical illness. This editorial is primarily focused on the prevention of depression among patients with physical illness.

The first study of this type was reported by Rovner *et al*[4] in which problem-solving therapy was administered in the patient's home over 8 weeks during six sessions to 105 patients age 65 years or older with a recent diagnosis of neovascular related macular degeneration in one eye and pre-existing age-related macular degeneration in the other eye (n=105) or usual care administered to comparable patients (n=101). Only 5 of the 206 patients had a prior history of treatment for depression. The 2-month incidence rate of depressive disorders in the therapy group was 11.6% *v.* 23.2% in the usual care group (odds ratio OR=0.39, 95% CI 0.17–0.92, P=0.03). At 6-month follow-up, however, the prevalence of depressive disorder was similar in both groups. The major limitation of this study was that it was single-blind study and some raters could not remain masked.

We recently reported the results of a randomised double-blind preventive intervention study of 176 patients without depression within 3 months following acute stroke.[5] Escitalopram-treated patients (n=59) (10 mg/day, age <65 and 5 mg/day, age $\geqslant 65$) were significantly less likely to develop depression during 1 year of treatment compared with patients given placebo (n=58) (8.5% *v.* 22.4%; adjusted hazard ratio HR=4.5, 95% CI 2.4–8.2, $P<0.001$). Patients who received non-masked problem-solving therapy (n=59) were also significantly less likely to develop depression than placebo-treated patients (11.7% *v.* 22.4%) (adjusted HR=2.2, 95% CI 1.4–3.5, $P<0.001$). Only three individuals in each group (total, nine patients) had a prior history of mood disorder. Prior history of mood disorder turned out to be a significant risk factor for depression (adjusted HR=5.2, 95% CI 3.3–8.1, $P<0.001$); however, 22 of the 25 cases of depression during the study were first ever episodes of depression.[4] The limitations of this study included a selected population of patients with stroke who met criteria for no other significant illness, or cognitive or comprehensive language impairment. The presumed prevention of 11 cases of depression (placebo cases minus treated cases) was among never-depressed individuals. Other investigators have also conducted preventive intervention studies for post-stroke depression.[6]

What type of preventive intervention is most efficient?

In a recent editorial on prevention of depression, Reynolds *et al*[7] stated 'indicated preventive interventions that target persons with elevated depressive symptoms may turn out to be a more efficient research paradigm and use of clinical resources, though that remains to be demonstrated'. This logical suggestion was based on the report of a longitudinal ageing study in Amsterdam in which Smit *et al*[8] reported that 158 incident cases over a 3-year period were identified from an at-risk group of 1925 individuals without depression at baseline. The study found that female gender, low education, two or more chronic illnesses, functional limitations, initial severity of depressive symptoms and a small social network were all significantly associated with an increased risk of developing depression. The incident rate ratio among individuals who had depressive symptoms, functional limitations, a small social network and were female was 4.6 compared with individuals without these factors. In the case of stroke patients, although each of these factors has also been associated with increased prevalence of post-stroke depression,[9] the only pre-treatment risk factor that was significantly associated with the development of depression in our preventive intervention study was previous history of mood disorder. The assumption that

factors other than depressive symptoms such as functional limitations, a small social network or female gender could be completely blocked by the use of antidepressant medications is an assumption that has not been demonstrated. Furthermore, the baseline severity of depressive symptoms in our preventive intervention study was not significantly different among the patients who developed depression during the preventive intervention compared with those who did not develop depression. Thus, whether indicated, selective or universal preventive intervention will be the most productive strategy, as Reynolds *et al*[7] thoughtfully stated, 'remains to be demonstrated'.

This progress, however, raises two questions that will be essential to our assessment of the role of preventive intervention in psychiatry. First, what will be the measure of preventive success and will this vary over time? Will our primary goal be to reduce the number of cases and therefore the psychological suffering associated with depression or alternatively should we target the morbidity and mortality that have been associated with depression following physical illness[10] or some other outcome measure? These adverse effects of depression on recovery, morbidity or mortality have already been shown to be reduced by the use of antidepressant medication.[6,11,12] Thus, perhaps these alternative measures of outcome would reflect a more useful picture of preventive intervention than the rates of incident depression. Furthermore, the time when we measure outcomes may be as important as the measures themselves. Some of the most positive effects of preventive intervention may take years to manifest themselves. For example, in a study of 104 patients with and without depression[11] with acute stroke given fluoxetine (20–40 mg/day) or nortriptyline (50–100 mg/day) over 12 weeks, the mortality rate at 7–9 years follow-up was significantly lower in both groups given antidepressants (i.e. 42 survivors of 71 patients, 59.2%) compared with placebo (i.e. 12 survivors of 33 patients, 36.4%) (χ^2=8.2, d.f.=1, P=0.004, log rank test). Kaplan–Meier survival curves, however, did not show a significant effect of preventive intervention on mortality until 3 years following treatment. Thus, our current preventive intervention studies of 8 weeks[4] or even 1 year[5] can identify the rate of depression, quality of life and social function, but ultimately these may not identify the most important benefits of preventive intervention and therefore lead to incomplete or even false assessments of success.

The other question which deserves some reflection is whether studies, even among those with physical illness, should continue to focus on either indicated or selective preventive intervention as compared with universal preventive intervention. Although researchers in the field have tended to dismiss universal preventive intervention as economically impractical, a recent simulation study[13] in coronary heart disease (CHD), found that high-dose use of simvastatin in patients with hypercholesterolaemia would result in a 7.2% reduction in CHD events and low-dose universal use of simvastatin would result in a 25% reduction in CHD events. Thus, only a fraction of the targeted events (e.g. perhaps depression) would be prevented with selective or indicated prevention, because not all patients who will manifest CHD (or perhaps depression) have the risk factors or are part of a high-risk group. Universal prevention would, therefore, lead to a substantially higher success rate. Perhaps 3 months of antidepressants administered to 20- or 30-year olds with no physical illness or history of mood disorder or to 60-year olds might block the effects of subsequent depressions or physical illness with associated depression on morbidity or mortality?[14] Obviously only empirical data can answer these questions, but as preventive interventions in psychiatry continue to emerge, we should not set our sights too low or conclude that we cannot achieve the higher success rates associated with universal prevention.

Whichever method turns out to be more widely used, researchers in this field have already shown that first-episode depression can be prevented in patients with a physical illness who have never previously had an episode of depression. Clearly, further studies of prevention in psychiatry are needed and perhaps, ultimately, we will be able to spend as much time preventing disorders as we do treating them. One thing seems likely. The large number of patients at high risk for depression owing to their physical illness who currently do not receive interventions for their depressive disorders[15] will be reduced by the use of preventive intervention strategies in psychiatry.

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