

# Preventing depression in high-risk groups

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## Purpose of review

Although most would agree that to prevent is better than to cure, prevention of depression has only recently been studied rigorously. The purpose of the present study is to review the state of the current literature.

## Recent findings

The technical and theoretical literature underpinning depression prevention is developing in concert with high-quality intervention studies testing the effects of novel preventive interventions. Data suggest that universal prevention, targeting the whole population, is not likely to be effective, whereas both selective (high-risk groups) and indicated (people with some signs or symptoms, but no disorder) prevention may be very effective. Overall, preventive interventions may reduce the onset of depression by as much as 25–50%, which compares favourably with treatment.

## Summary

Preventing depression may be effective at all ages and in diverse settings. Prevention has moved beyond the stage of pioneering studies and it deserves a regular place within our armamentarium to combat depression.

## Keywords

depression, effects, epidemiology, prevention, randomized controlled trial

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## Introduction

The twentieth century has seen enormous changes in the prevalence and consequences of disease. In most of the Western world, both in the area of infectious disease and in cardiovascular medicine, spectacular downtrends have been achieved. Disentangling, in retrospect, how or why this has been brought about is fraught with difficulties. Public awareness, education, social change, financial investment, scientific progress, prevention, treatment and plain hard work, acting in concert, have each made their contributions. Compared with this, where are we in mental health? It is fair to conclude that we are far from a situation in which we can say that mental illness is under control, or that we are able to show downtrends in the onset or public health consequences of mental disorder. Indeed, given the changing demands modern societies impose on the mental vitality of their citizens, the tolerance for mental dysfunctioning is decreasing quite rapidly.

The present study is written with a firm conviction that prevention is a prerequisite for our making any meaningful difference towards the societal harm and burden imposed by depression. Given that conviction, the recent literature will be used to address a number of questions. First of all, is depression a good candidate for prevention and why is it unlikely that other strategies, such as treatment, will prove to be sufficient to curb the burden

of depression? Strategies to prevent the onset of disease may be directed towards the whole population (universal prevention), selected high-risk groups (selective prevention) or towards those who have already developed some signs or symptoms but have not (yet) developed the full-blown disorders (indicated prevention). The study will be limited to these three types of prevention and discuss which strategy may prove most fruitful, given the limitations in the real world (such as limited resources). The idea that it is better to prevent than to cure is as old as medicine itself. However, rigorous testing of interventions as to their effectiveness in preventing the onset of depressive disorders is a relatively young and as yet under-explored area of science. Our third aim is to review data from randomized controlled studies in the area of preventing major depression.

The conclusion will be that, for many reasons, we should learn from what has happened in other areas of medicine, such as cardiovascular health, integrating prevention while working towards curbing the deleterious effects of depression.

## Why is depression a good candidate for prevention?

Given that prevention works to lower the onset of a disease, it is especially suited for high-influx disorders.

In a high influx disorder, the ratio between recent-incidence and prevalence is high, which means that a relatively large proportion of patients have only recently developed the disorder. The natural history of depression is extremely varied, but community studies show that about 50% of those with major depressive disorder (MDD) remit within 3 months. The remittance curve flattens out further on, leaving about 20% who have not remitted within 1 year [1]. This means that depression is indeed a high-influx disorder. Combined with a high prevalence, a huge impact on public health and the fact that depressive episodes can develop at all ages, there is a good case for community strategies to prevent depression.

However, prevention may be both expensive and cumbersome, whereas there are several effective treatments. Predicting who will become depressed will never be perfect, so why not wait for people to become depressed and then offer treatment? Andrews *et al.* [2] have explored, in scenario studies, the effect current treatments may have on the public health burden of mental disorders. Even if we were able to reach all patients with MDD, and if we were able to offer every patient evidence-based treatment, only 40% of the burden of mental disorders would be averted. This would mean that there is not only a good case for attempting to prevent depression, but prevention is also a necessary condition to curb the effects of depression on our patients and on society.

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### What strategies may work best?

The question of which type of intervention may be most effective will be addressed below. Here we discuss at which point in the natural history of depression, and in which people or which part of the population, we may most (cost)effectively intervene.

Cuijpers [3] showed that it is practically impossible to test whether universal prevention (preventive intervention aimed at the whole population) is effective in reducing the onset of depressive disorders. Sawyer *et al.* [4\*\*] have completed a school-based intervention to prevent depression in adolescents. This was a universal intervention in which, over a 3-year period, the curriculum, the school climate, care pathways and contact with the community were targeted. A large number of schools (25 pairs), including over 5000 students, were randomized. However, no effects were evident on depressive symptoms and the article draws attention to the difficulties inherent in universal prevention. A further example of universal prevention is the use of food supplements in the hope of reducing the onset of depression. Van de Rest *et al.* [5\*\*] conducted a three-arm randomized controlled trial (RCT) testing whether low or higher dose supplementation with n-3 polyunsaturated fatty acids (PUFAs) would help to prevent depression among healthy older people in the

community. Over 26 weeks, 302 older participants were randomized to consume placebo, 400 mg or 1800 mg doses of PUFA. Although the plasma concentrations demonstrated high intake fidelity, there were no effects at either the 13 week or 26 week evaluation.

With regard to selective and indicated prevention, community-based cohort studies are the best we have to identify high-risk groups and work out what the costs and benefits may be if these people were approached with a preventive intervention. In both younger and older adults, it turns out that no single known risk factor for depression is preferred [6,7]. However, using different combinations of risk factors, subgroups can be identified, in which the *a priori* risk of developing depression is high, that represent as sizeable a proportion of all future depression in the community as possible, while involving as small a percentage of the population as possible. The results suggest that both selective and indicated prevention may be economic [7,8]. This is a young and relatively unexplored area. It is conceivable that combinations of known risk factors with biological markers or genetic material will greatly enhance the precision of prediction. The relevance of this is that it would reduce the number of people who are exposed to preventive intervention who would never have developed depression if not approached (false positives).

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### Effects of randomized studies among high-risk groups

A number of RCTs rigorously testing the effects of prevention of depression were recently completed.

#### Selective prevention

Pitceathly *et al.* [9\*\*] conducted an RCT to test whether a brief psychological intervention may help to prevent anxiety or depressive disorders among patients recently diagnosed with cancer. This was a large (465 patients were recruited, of whom 313 completed the study), well conducted trial, testing whether the brief intervention would be effective and whether the timing of the start of the intervention may make a difference, while stratifying the participating patients with regard to their *a priori* risk for depression and anxiety. After 12 months there was no overall difference between those exposed to the intervention and the controls. However, among patients at high risk for depression or anxiety the intervention was effective [odds ratio (OR) = 0.54, 95% confidence interval (CI) 0.29–1.00], whereas in the low-risk patients there was no difference. This would again suggest that universal prevention (which includes people at low risk) is not a preferred strategy for preventing depression.

Robinson *et al.* [10\*\*] tested the effect of escitalopram and problem solving to prevent depression in patients with stroke. The rationale was that more than half of the

patients experiencing a stroke develop depression. This is an example of selective prevention, targeting a group at high risk due to a physical illness. Within 3 months after a stroke, 176 nondepressed patients were randomized to receive escitalopram, placebo or problem-solving therapy (PST). Over the 12-month intervention period, the patients receiving placebo were significantly more likely to develop depression than either those receiving escitalopram [hazard ratio (HR) 4.5; 95% CI 2.4–8.2] or those receiving PST (HR 2.2; 95% CI 1.4–3.5).

A comparable study was done by Rovner *et al.* [11], testing the effect of PST among patients with macular degeneration. The rationale for this study was that age-related macular degeneration leads to irreversible loss of vision and disability, which carries a high risk of concomitant depression. In this RCT, 206 patients with existing macular degeneration in one eye plus a recent manifestation in the other eye were randomized to either care as usual or PST (eight weekly sessions). After 8 weeks, the incidence of depressive disorders was less among those exposed to PST (HR 0.39; 95% CI 0.17–0.92), and those in the PST arm were less likely to have relinquished valued activities.

De Jonge *et al.* [12\*\*] administered a multifaceted nurse-led intervention to prevent major depression in 100 patients with diabetes or rheumatic disease who were considered to be medically complex. At 1-year follow-up the incidence of depression in those randomized to the intervention was 36%, as compared with 63% in the usual care group.

#### Indicated prevention

Garber *et al.* [13\*\*] described a RCT to test the effect of preventing depression in at-risk adolescents. The rationale for this study was that adolescent children of depressed parents are a high-risk group, which may be targeted for prevention. A large multicentre RCT was conducted, including 316 adolescent offspring of parents with depressive disorders. The adolescents were included whether they either had a history of depression or had elevated but subthreshold levels of symptoms. This is an example of a strategy of combining risk factors in order to reach a well defined group with a very high *a priori* risk of developing depression. The adolescents were randomized to care as usual, versus a cognitive behavioural group consisting of eight weekly sessions. Over the 6-month follow-up, the risk of developing depressive episodes was significantly and considerably reduced (HR 0.63; 95% CI 0.40–0.98). Among adolescents whose parents were not depressed at the time of the intervention, the effects of the intervention were considerably stronger than among adolescents whose parents were depressed at the time.

A further recent trial was conducted among elderly patients in primary care. Van't Veer *et al.* [14\*\*] tested

the effect of a stepped care programme to prevent depression and anxiety in older people. The rationale in this trial was that older people with subthreshold symptoms but no full-blown disorder are at very high *a priori* risk to develop disorders. However, even in this group the majority (70%) do not go on to develop full-blown disorders [15]. Therefore, it may be both economical and ethically important to adopt a stepped care approach in the design of preventive intervention. In this way, all those who are eligible would receive an easy to apply and user friendly intervention, whereas only those who do not respond are offered more intensive treatment. Moreover, as the risk factors for depression and anxiety overlap, interventions that prevent depression are also likely to affect the onset of anxiety disorders.

In this RCT 170 patients with subthreshold symptoms were randomized to either care as usual or a four-stage stepped care prevention programme. Each of the steps lasted for 3 months and included watchful waiting, guided self-help, problem solving and referral to the general practitioner (GP) for further evaluation or treatment. Over the year the intervention lasted, it was successful in reducing the incidence of Diagnostic and Statistical Manual of Mental Disorders (DSM) anxiety or depressive disorders (HR 0.49; 95% CI 0.24–0.98). The stepped care strategy was also effective in that only a small minority were referred to the GP to step up the treatment and that it did not require extra use of psychoactive medication.

#### Novel ways to reach large numbers of people at low cost

In order to be able to make a true difference in public mental health, prevention needs to be designed in ways that may reach large numbers of people at low cost. The internet is potentially an ideal way to reach large numbers of people at risk for depression. This may be especially true for younger people. Van Voorhees *et al.* [16\*\*] reported the results of a large RCT testing the effects of an internet-based prevention programme for adolescents. They included adolescents with subthreshold depressive symptoms, implying that this was an indicated prevention trial. Participants were randomized to either motivational interviewing, as conducted by the physician, or participating in an internet-based preventive intervention for depression. The experimental group was less likely to develop a depressive episode by 12 weeks (4.65% versus 22.5%;  $P=0.23$ ). The uptake of the intervention was very high (>90%). Another way to reach large numbers of people at low cost is to use trained lay personnel. A recent example is the study by Dennis *et al.* [17\*\*], which evaluated the effects of telephone-based peer support on the onset of postnatal depressive disorders. They randomized 701 pregnant women, comparing peer support with care as usual, and found a reduction of relative risk (RR) of 0.46 (95% CI 0.24–0.62). Further examples of strategies that

may be very cost effective and have recent positive trial evidence are to expose elderly inhabitants of nursing homes to bright light [18\*\*] or to train nursing staff in contact with patients recently diagnosed with cancer to enhance their communication skills [19\*\*].

These results are in line with those of a recent review summarizing the effects of earlier studies aiming to prevent the onset of depressive disorders. In the present study, Cuijpers *et al.* [20\*\*] conducted a meta-analysis of 19 RCTs that met rigorous inclusion criteria. On average, the interventions were able to reduce the onset of depression by 22%.

## Conclusion

Prevention of depression is a young, but rapidly evolving field. The present study demonstrates that the technical and theoretical basis for prevention is developing in concert with new and effective interventions. This study has attracted a good number of excellent research groups from all over the world, working in all age groups and in diverse settings. The current data indicate that focusing attention on high-risk groups is likely to be more fruitful than adopting universal preventive strategies. Epidemiological data can be used to select high-risk groups in whom prevention may be most fruitful. Combining the existing epidemiological data with biomarkers or genetic data may be a way forward for the near future. Considering the effectiveness of prevention, a risk reduction ranging between 25 and 50% has been found in recent reviews and studies. This compares favourably with treatment, in which the difference between active treatments and placebo are typically found to be in the same range. Reaching the very large numbers of people at risk in the community in an ethically acceptable and affordable manner is one of the many problems that need to be addressed in the near future. Embedding effective preventive strategies in existing healthcare arrangements, training health personnel, recruiting trained lay volunteers and adapting the environment (as in the bright light trial) may represent solutions to this. Exploiting the potential of new and evolving media, such as the internet, may be a very potent way to reach those at risk in a comfortable way. It appears that prevention of depression has passed the stage of the pioneer studies and that it deserves a regular place within our armamentarium to combat depression.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 70–71).

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