

Most patients need several sequential treatment steps for remission of major depression

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Major depressive disorder is a major public health problem that affects 7% of the population during any 12-month period and affects around 1 in 6 people throughout their lifetime. A Seminar published Online First by the *Lancet* reviews recent developments relating to this seriously disabling condition, and concludes that most patients need several sequential treatment steps for remission of their major depression. The Seminar also explains why deep brain stimulation is a treatment that holds promise for the future. It is written by Professors David J Kupfer, Ellen Frank, and Mary L Phillips, all of University of Pittsburgh Medical Center, PA, USA.

Depression has a similar negative impact on health equivalent to other [chronic diseases](#), such as arthritis and diabetes, but this is not always recognised. Furthermore, it can combine with any other chronic disease to result in substantially worse [patient outcomes](#). The authors say: "A crucial implication is that primary care providers should not ignore the presence of depression when patients have a chronic physical disorder." They add that some of the risk factors for obesity might also increase the risk of depression and, in turn, depression increases the risk of becoming obese. Such two-way relationships might be the reason for increased association between depression and [coronary artery disease](#). Studies have also led to the conclusion that [clinical depression](#) is associated with a 65% increased risk of diabetes in elderly people.

The evidence continues to suggest that drug treatments and depression-specific psychotherapy are both effective treatments for depression, either alone or in combination. [Cognitive behavioural therapy](#) and interpersonal psychotherapy are also backed by several large studies in the USA and Europe, and [cognitive therapy](#) can be delivered using non-traditional means such as telephone or internet, which can lead to large cost savings. The authors also point out antidepressants are the most commonly prescribed type of medication in both general practice and hospital outpatient-based practice, but not all sectors of the population are accessing them equally, with low rates of use persisting in racial and ethnic minorities.

The authors refer to the STAR*D study that examined up to four successive treatment steps, starting with citalopram, and included a switch to and augmentation with additional drug or cognitive therapy in the subsequent steps. Remission rates in steps 1 to 4 were disappointing at 37%, 31%, 14%, and 13%, with a cumulative remission rate of 67%, lower than suggested by efficacy studies of the various antidepressants. The authors say this "suggests that, in actual practice, most patients need several sequential treatment steps to achieve [remission](#)." They also mention new strategies that have been used, such as ademetionine for [major depression](#) and intravenous ketamine for the acute treatment of treatment-resistant depression.

The safety of selective serotonin reuptake inhibitors (SSRIs) has been much discussed, but the authors say the evidence is conflicting in relation to suicide risk and use of these drugs, with some studies showing an increased risk and others showing reduced risk of suicide after starting SSRI treatment, especially with sertraline, and in men. They also discuss risk of SSRI use during pregnancy, with data showing that paroxetine might cause major malformations, especially cardiac defects. Presence of persistent pulmonary hypertension in newborns can be associated with SSRI use in late pregnancy, and infants with

continuous exposure to mother's depression and continuous exposure to SSRIs throughout gestation were more likely to be born preterm than were infants with partial or no exposure. The authors say: "Guidelines suggest that SSRIs should be used with caution during pregnancy and that paroxetine be avoided."

An exciting prospect for future treatment for major depression is use of [deep brain stimulation](#), yet to be approved by the US Food and Drug Agency (FDA) or the European Medicines Agency, but showing promising results. Electrodes are implanted bilaterally in the brain and are connected to an internal pulse generator, that can be adjusted to the patient's needs. Transcranial magnetic stimulation (TMS) already has FDA approval, but repetitive TMS might not be as effective as deep brain stimulation.

However, the authors conclude that, despite the recent clinical, neurobiological, and treatment advances made in the past five years, "no fully satisfactory treatments for major depression are available".

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