

Overview: a brief summary of current and future treatments for depression

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Treatments for depression have come a long way from what was practised in ancient times, the Middle Ages and the early part of the 20th century. From Hippocrates (400 BCE) suggesting balancing the body fluids, or humours, to exorcisms, drowning and burning in Europe during the Middle Ages, to talking therapies, electric shock treatments and even lobotomies (in extreme cases), the search for an effective treatment for depression, without unwanted adverse effects, continues.

With emerging scientific knowledge, the mid 20th century witnessed the introduction of drugs described as antidepressants, which helped to alleviate the symptoms of depression in many sufferers, though not in all, and not without adverse effects. Therefore, the quest for a perfect antidepressant, effective and free of adverse effects, has continued well in to the 21st century, without major success.

In parallel with some of these developments, mostly refinements of existing antidepressants, there has been progress with developments in other so-called biological treatments. Brain stimulation techniques, such as electroconvulsive therapy (ECT), have been refined and made more humane with the use of anaesthesia. The introduction of other neurostimulation techniques, such as deep brain stimulation (DBS) in the 1950s, transcranial direct current stimulation (tDCS) in the 1960-70s, repetitive transcranial magnetic stimulation (rTMS) in the 1990s, and vagus nerve stimulation (VNS), have added powerful therapeutic tools to the array of antidepressants. Continued advances in these neurostimulation techniques have resulted in wider acceptance, along with approval from agencies such as the FDA (USA) and NICE (UK), leading to greater use in clinical practice in both private, as well as national, health services.

There has also been expansion of so-called talking therapies, which may incorporate behavioural techniques. Some of the widely-practised talking therapies include cognitive behavioural therapy (CBT), dialectic behaviour therapy (DBT) and psychodynamic therapies, with CBT having a large evidence-base for mild-to-moderate depression.

Currently, individuals diagnosed with depression in the UK receive treatment that follows a stepwise approach. Depression described as mild-to-moderate is usually managed by GPs with or without the help of therapists specialising in various forms of talking therapies. However, this is not always possible given the limited availability of such therapists, and often results in the prescribing of antidepressants, which may not be appropriate and/or adequately monitored. Those experiencing moderate-to-severe depression should be seen by psychiatrists. Unfortunately, this is not always possible and, even among patients who are seen by psychiatrists, some may not fully recover due to the complexity of their illness, the influence of complicating factors, or the lack of availability of effective treatments.

Given the complexity of the phenotype of depression, and the current lack of understanding at the molecular level, it is not surprising that a drug acting on, for example, a discrete number of neurotransmitters might fail to be effective. When talking therapy and antidepressant medication together fail to help, combining antidepressants, augmentation strategies, for example with lithium or other mood stabilisers, and ECT may be tried. In some specialist centres (private or government funded) the brain stimulation techniques mentioned above are being offered with varying success. An unusual drug, ketamine, has been found not only to be very effective in treatment-resistant cases, but also to be fast-acting - within hours - in terms of alleviating depressive symptoms. This drug currently remains experimental, for use in treatment-resistant depression, and is available in only a few specialist centres.

While, in developed countries, the treatment of depression is not ideal, on a global level, unfortunately, depression often goes unrecognised, especially in the developing world, with millions remaining untreated or, indeed, under-treated.

Mental health disorders such as depression are highly complex, are influenced by biopsychosocial factors and can present in many guises. Effective management continues to rely on accurate exploration of symptomatology and an understanding of depression's effect on the individual's day-to-day living. Although the clinician always strives for the goal of effective management, given the somewhat limited current understanding and the lack of availability of highly effective therapeutic tools, further research is needed on all fronts. The aim of this research will be to increase understanding of causative factors (biopsychosocial) and pathophysiology (not just in the brain), and to develop both diagnostic markers and treatment markers so that the progress of treatment can be monitored.

Through improvement in imaging techniques, great advances have been made in identifying the regions and neuronal circuits of the brain involved in depression. However, the findings are not consistent in all cases of depression, and they do not yet guide us with regard to effective treatments.

While a genetic predisposition to depression is well established, the role of genetics in depression is quite complex, although knowledge continues to expand. If it is possible to define certain forms of depression as being purely genetic in nature, this will raise the possibility of using gene therapy.

Genetic knowledge can also help to achieve effective, and targeted, use of antidepressant drugs. Currently antidepressants are usually chosen on the basis of their efficacy and side-effect profile; the choice often depends upon the experience of the prescriber. There is the intriguing possibility of patients being able to present to clinicians with their genetic profile in the not so distant future, to allow for a more targeted approach. This approach should increase the likelihood of a particular antidepressant being effective, not only by eliminating the guesswork in choosing a particular antidepressant, but also shortening the time lag to remission.

The emerging science of epigenetics also holds great promise in unravelling the causes and development of depression, particularly in individuals who have either experienced trauma (physical, emotional and/or sexual) in their childhood or who have a family history of childhood trauma.

Research into brain-derived neurotrophic factor (BDNF) has shown its important role in neuronal survival and growth, neurotransmitter modulation and neuronal plasticity. It is interesting to note that BDNF levels are raised both by exercise, increasingly recommended for depressed individuals, and by treatment with antidepressants. This raises the possibility of the use of BDNF as a treatment marker for the treatment of depression.

Research is also beginning to explore the possibility of immune dysfunction being the basis of depression, at least in some cases, hence searching beyond the brain may provide possible answers. Indeed, some research is beginning to support the use of specific anti-inflammatory drugs to treat certain forms of depression, and the measurement of inflammatory markers to monitor the progress of treatment. This offers the possibility of opening new avenues for further exploration in the fields of diagnosis and treatment of depression.

The use of the internet for clinical assessment, treatment, for example by CBT, and monitoring, sometimes described as e-mental health, is being developed and expanded at an ever increasing pace. There are now thousands of smartphone apps available. These can not only help with diagnosis, but are also being put forward as having a role in the treatment and monitoring of depression.

Current scientific knowledge, for example the role of certain foods having anti-inflammatory properties, exercise positively effecting BDNF levels, and recreational drugs (with some exceptions) and alcohol having negative effects, suggests the need for further research into life-style measures such as diet and exercise in both preventing and helping with the treatment of depression. With fascinating discoveries being made with regard to the role of the gut microbiome in influencing mental health, the importance of "life-style mental health" is beginning to be promoted by the scientific community.

In conclusion, although great progress has been made, there is still enormous scope for research, not only to increase our understanding of the complexities of depression, but also to provide fast and highly effective treatments that are free of adverse effects and which will alleviate the huge personal, familial, economic and societal burden of depression.