Recent developments and current controversies in depression

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In this review of the last 5 years' developments in research into depression we focus on recent advances and current controversies. We cover epidemiology and basic science as well as the treatment of depression in adults in all its forms. Depression in childhood and adolescence, as well as in old age has been covered in recent Seminars in *The Lancet*. Depression in adulthood remains a very common and under-treated condition, resulting in a high degree of disability. Increasingly detailed knowledge about impairment of information processing in depression is being supplemented by quantitative studies of the brain processes underlying these impairments. Most patients improve with present treatments. The mechanisms of action of antidepressants are not fully understood; the hypothesis that reversing hippocampal cell loss in depression may be their active principle is a fascinating new development. Moral panic about the claim that antidepressant serotonin reuptake inhibitors cause patients to commit suicide and become addicted to their medication may have disconcerted the public and members of the medical profession. We will try to describe the considerable effort that has gone into collecting evidence to enlighten this debate.

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Compared with other medical diagnoses, depression is very common. It occurs twice as frequently in women as in men, can begin at any age, but has its average age of onset in the mid-20s.[1] Lifetime prevalence estimates for major depressive disorder (panel) in the community range from 15% to 17% (95% CI),[1] 12-month prevalence from 6% to 7% (US national comorbidity replication; n=9090).[2,3]

Major depressive disorder impairs the ability to function, leading to role impairment in well over 50 % of patients.[2] Role impairment is likely to be a direct corollary of depressed mood.[4,5] Effective treatment is therefore of the essence. Unfortunately, only 46–57% (95% CI) of the 12-month cases in the USA were receiving health care treatment for major depressive disorder, and only 18–25% were adequately treated.[2] In a European community survey (n=5993), 25–38% of men and 21–30% of women interviewed and classified as having major depressive disorder used any health services in the past 12 months for their depression. This percentage rose to only 35–49% of those with severe major depressive disorder.[6] Any discussion of the epidemic rise in prescriptions of antidepressants together with popular scepticism towards anti-depressant treatments has to be considered against this background (figure 1). Depression is especially common in many non-psychiatric medical settings, such as inpatients wards, in chronically ill patients and during the recovery from acute medical illness.[7]

A crucial aspect of the epidemiology of major depression is the increased mortality associated with this condition. A recent meta-analysis of 25 studies with 1·3–16 years' follow-up of over 100 000 individuals reported an overall relative risk of dying between 1·58 and 2·07 (95% CI) compared with people who are not depressed.[8] The relative risk in subclinical depression was not substantially smaller than in clinical depression. The analysis did not examine potential confounders, such as chronic illness or lifestyle. The mechanism of increased mortality is therefore not clear. A major contribution to increased mortality in depression will come from the risk of suicide in this patient group. Traditionally, lifetime risk (ie, proportionate mortality: the percentage of the dead who died by suicide during follow-up) is reported between 15% and 19%.[9,10] This figure is likely to be inflated, especially if the period of follow-up, typically after an acute episode in hospital, carries a higher risk of suicide than periods further removed from the index episode.[11]

Another modifying factor is the diagnostic system: early versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM), for example, drew the boundaries of depression much narrower than DSM III or IV, which include many milder forms of the illness. A recent review[11] took account of the treatment setting of patients and identified a clear hierarchy of risks, with estimates of lifetime prevalence of suicide being highest in suicidal inpatients (8·6%), lower in other inpatients (4%), and lowest amongst outpatients with affective disorder (2·2%). Even with these revised figures the risk of suicide rises over background levels from four-fold in depressed outpatients to 16-fold in patients with affective disorders admitted because of suicidal risk.[11]

A sixth of people in the community will have major depressive disorder during their lifetime. Only between a quarter and half of patients will be in contact with the

Search strategy and selection criteria

We searched MEDLINE, and for some topics EMBASE and PsychInfo, initially limiting the search to systematic reviews and meta-analyses, then if necessary to controlled studies. Recent national guidelines and reports were also reviewed.

For **recent coverage of depression in *The Lancet*** see *Lancet* 2005; **365:** 1961–70 (in elderly people); and *Lancet* 2005; **366:** 933–40 (in childhood and adolescence)

health services for their depression. In half the cases, the illness is incapacitating, leading to role impairment at work or at home. The risk of premature death is increased, in part because of a greater risk of suicide.

Causes and associations

Genetics and pharmacogenetics

There is no doubt that genetic factors have an important role in the aetiology of depression. Heritability has been estimated from twin studies as 31–42%, with a substantial contribution of environmental effects unique to individuals (including measurement error) of 58–67%.[12] Depression with recurrent episodes and possibly early onset may be associated with greater familial aggregation.[12]

Traditional genetic linkage studies and candidate gene methods have been used with fairly limited success in major depression.[13] Genetic models of aetiology generally assume a large number of genes with relatively small contributions to liability. Advances in high-throughput genotyping and microarray techniques have made it more feasible to identify genes with small effect sizes.[13] Of special clinical interest are those studies that are based on pathophysiological notions (candidate genes), and in particular those that examine the probability of patients to respond to particular treatments.

Brain-derived neurotrophic factor may have a central role in the effectiveness of antidepressants, but there is no firm evidence of an association of its alleles with major depressive disorder.[14–16] Monoamine oxidase A is involved in the metabolism of catecholamines and is the target of one group of antidepressants, the monoamine oxidase inhibitors. Certain monoamine oxidase A gene promoter polymorphisms are found in subgroups of patients with major depression; they are by no means specific to depression, but also occur in patients with anxiety.[17,18] The catechol-O-methyltransferase (another catecholamine metabolising enzyme) Val108/158Met polymorphism has been intensively investigated in psychotic disorders, but has also been associated with treatment response to mirtazepine, but not paroxetine, in major depression.[19] Human tryptophan hydroxylase-2 (hTPH2) is involved in the synthesis of serotonin. The theory that it is the rate-limiting step of serotonin synthesis is supported by the occasional success of the augmentation of antidepressants with tryptophan.[20] A single nucleotide polymorphism in its gene with roughly 80% loss of function is associated with major depression, but not with bipolar illness.[21]

The most frequently examined candidate gene codes for the serotonin transporter, which is the drug target of serotonin reuptake inhibitors, such as fluoxetine. A 44-bp insertion or deletion results in a long (l) and a short (s) variant of this gene; the s-variant is associated with a two-fold decreased expression and transport activity in vitro. Individuals in an epidemiological sample with one or two copies of the short allele of the serotonin transporter promoter polymorphism showed more depressive symptoms, diagnosable depression, and tendency to commit suicide in relation to stressful life events than individuals homozygous for the long allele.[22] Unfortunately, two subsequent twin studies were not concordant in lending support to this result.[23,24] The importance of the s-variant of the gene for stress susceptibility is supported by an increased amygdala response to stimuli of threat during a functional MRI study and an increased prefrontal response to an error processing task in healthy volunteers.[25,26] The association of serotonin transporter alleles with hippocampal size is more complex and seems to be related to age of onset.[27,28] Patients with two alleles of the l-variant generally show a better clinical response to serotonin reuptake inhibitors in studies of mainly white patients.[29,30] The other serotonin transporter polymorphism described has a variable number of tandem repeats (9, 10, and 12 copies)

Panel: **ICD-10 criteria for depression**[3]

Depressive episode

At least two weeks of: depressed mood, loss of interest and enjoyment, reduced energy, increased fatiguability, diminished activity, reduced concentration and attention, reduced self esteem and self confidence, ideas of guilt and unworthiness, bleak view of the future, ideas or acts of self-harm, disturbed sleep, diminished appetite

Mild depression

Two of depressed mood, loss of interest and enjoyment, reduced energy, and two others

Patient will not cease to function completely

Moderate depression

Two of depressed mood, loss of interest and enjoyment, reduced energy, and at least three others, some at marked intensity

Considerable difficulty functioning

Severe depression

Two of depressed mood, loss of interest and enjoyment, reduced energy, and at least four others, some of severe intensity, plus considerable distress and agitation, or psychomotor retardation; sometimes with psychotic symptoms, such as hallucinations or delusions

Dysthymia

Depression of mood which is never or only very rarely severe enough to fulfil the criteria for recurrent depressive disorder, mild or moderate severity

Very long-standing

Usually begins in early adult life, lasts at least for several years

Low mood varies little from day to day, is often unresponsive to circumstances, yet may show a characteristic diurnal variation. Anhedonia is a core feature of all depressive illnesses. Anxiety symptoms and weight loss are common. If episodes of mania or hypomania occur, the illness is called bipolar affective disorder.

located in intron 2 of the gene. There may be a better response rate in 12/12, as opposed to 10/12 patients, but this improved rate has only been shown in Asian studies.[29,30] A recent search for pharmacokinetic effects of *CYP2D6* and *CYP2C19* alleles suggested that for 14 of 20 investigated antidepressants, at least a doubling of the dose would be needed in extensive metabolisers compared with poor metabolisers. This variation in effects does strengthen the argument for antidepressant plasma monitoring in depression resistant to treatment.[29] Although promising and fascinating, the prospective practical application of such genetic and pharmacogenetic information is still some time away.

Heritability of depression has been estimated to range from 30–40%. Because of its pattern of inheritance, but also because of heterogeneity of clinical samples, no genes of major effect have been identified. A multitude of genes with small effects are likely to be identified, which will be related to certain aspects of genetic vulnerability to depression and will work alongside or interact with environmental factors.

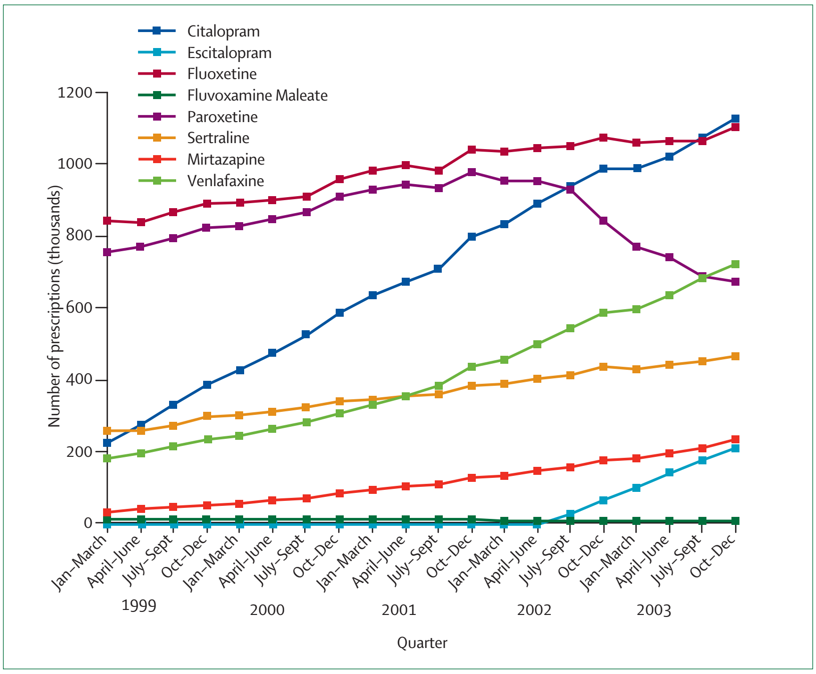

Figure 1: **Prescription cost analysis data for new antidepressants**
Figure produced from data from the UK prescription pricing authority, for all age groups 1999–2003. (UK Department of Health, Statistics Division 1E, Prescription Cost Analysis system.)

Changes in cognitive performance

Most people now accept that major depressive disorder is associated with cognitive impairment. Episodic memory seems to be the main aspect of cognitive functioning that is vulnerable to the negative effects of depression.[31–33] Temporal lobe lesions typically disrupt episodic memory. Since hippocampal atrophy has been shown in patients with major depressive disorder,[34] impaired episodic memory function in depression might be associated with dysfunction of the hippocampus.[35,36]

Factors that can affect episodic memory in depressive disorders are depression subtype, severity, and age. Although this topic has been widely researched, findings have been equivocal. In one study, major depression and mixed anxiety-depressive disorder were associated with greater impairments than dysthymia, whereas in minor depression cognitive performance was unaffected.[33] In another study,[37] the number of depressive episodes was associated with verbal memory deficits, which could be an indication of sensitisation to the effect of depression with progressive cerebral dysfunction and anatomical changes.[35,38]

Further, psychomotor slowing and executive functioning—namely mental flexibility and attention—are impaired in people with depressive disorders.[33,36,38–40] Equally, updating of content—ie, working memory, set-shifting, and inhibition processes—are impaired in depressed patients compared with controls.[40] Psychomotor symptoms have been commonly associated with depressive episodes.[41] Since there is no objective evidence that psychomotor retardation is present in dysthymic patients this sign could be used to differentiate between dysthymia and major depressive disorder.[42]

The presence of cognitive abnormalities in some depressed patients is generally accepted now. From a practical point of view, they may interfere with activities of daily life, such as driving or working, but also with attempts to recruit cognitive processes for therapeutic purposes. The detailed analysis of cognitive data processing and its effect on mood and other dimensions of depressive symptoms have just started.

In vivo anatomical and functional brain changes

Most people now accept that hippocampal size measured by MRI is reduced in patients with unipolar major depressive disorder.[43,44] There is some discussion, however, about the clinical correlates of this change. Duration of illness, repeated episodes, treatment resistance (all partly overlapping) and previous abuse might be associated with hippocampal change.[35,43–45] Hippocampal atrophy has also been described in victims of abuse and of battle-induced post traumatic stress disorder.[46–49] Findings of animal studies suggest that increased glucocorticoid levels lead to impaired neurogenesis, excitotoxic damage or reduced levels of key neurotrophins in the hippocampus.[50,51] Of particular interest to the clinician, however, is that antidepressants can reverse these changes and that blocking hippocampal neurogenesis by irradiation can prevent the action of antidepressants in behavioural animal models of depression.[52–55]

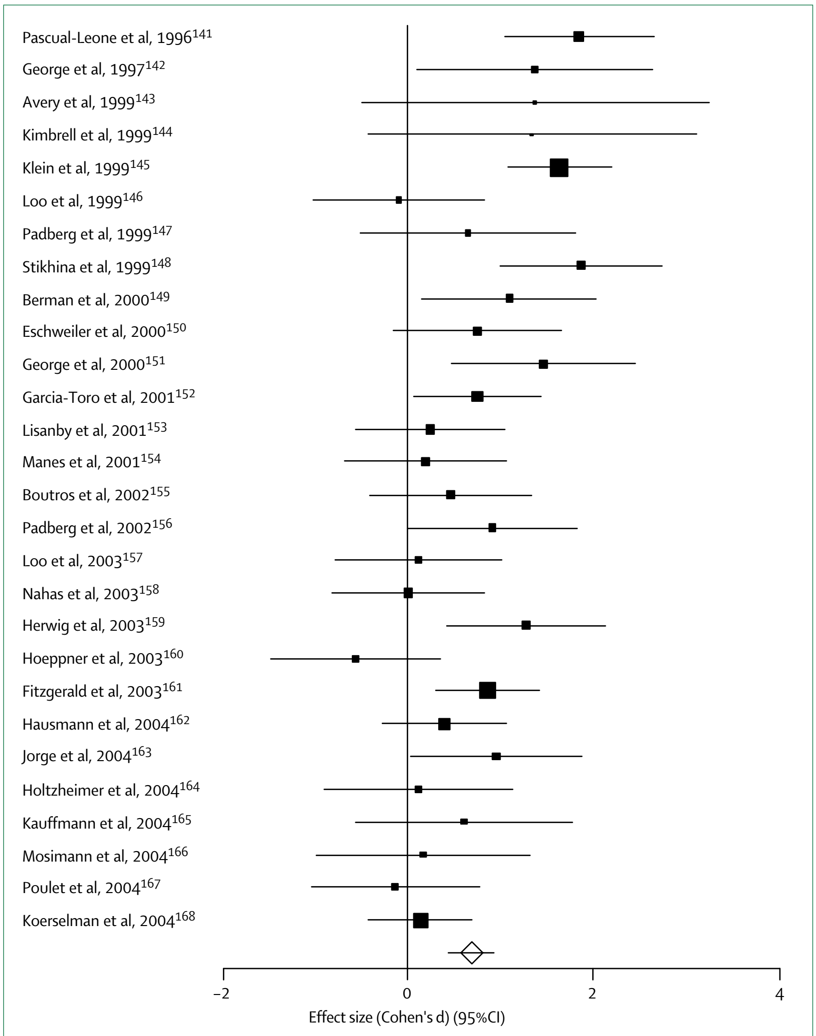

Figure 2: **Forest plot of controlled trials of transcranial magnetic stimulation in depression**
Information based on Burt and colleagues (2002),[140] and subsequently published papers.[141-168] Effect sizes (Cohen's d) were computed from changes in Hamilton or Montgomery-Asberg depression scores at beginning and end of treatment (2–3 weeks); when SD of difference scores were not available, SD of raw scores were used following Dunlap's suggestion.[169] Studies show sufficient heterogeneity (Q [non-combinability for d+]=60·82 (df=27), p=0·0002) to suggest that systematic modifying factors are at work and pooled effect size is not a reliable estimate. DL pooled effect size=0·680035 (95% CI=0·430108–0.929962).

Furthermore, hippocampal atrophy might be associated with cognitive impairment, in particular for episodic memory.[35,56] In the absence of larger longitudinal studies of depressed patients, whether the changes observed in hippocampus in cross-sectional studies are in fact the result of depression and stress (as postulated above), or whether they are the cause of certain clinical characteristics of the illness in the patients affected—such as treatment resistance or frequent relapses—remains to be resolved.[35]

Functional MRI (fMRI) is the method of choice to examine brain-behaviour relations. Anterior cingulate, orbitofrontal cortex, dorsolateral cortex, striatum, and medial temporal lobe have repeatedly been reported as abnormal in functional and structural imaging studies of depressed patients.[57–61] In healthy human beings and animals, the ventromedial prefrontal region is associated with emotional experience,[62,63] and the dorsolateral region with cognitive and motor function.[64,65] Findings of neuroimaging studies of mood disorder tend to show abnormally increased activity in emotion-related brain regions and underactivity in cognition-related regions.[59–61,66] Neurosurgery for treatment-resistant mood disorder (a very rarely used procedure) has long targeted the ventromedial prefrontal region, excluding the dorsolateral region, since dorsolateral lesions cause cognitive deficits. Recently, ventromedial prefrontal overactivity was reported to predict response to a neurosurgical procedure for treatment-resistant mood disorder.[67] In the following section we discuss fMRI studies of depressive illness reported in the past few years. All the studies explore possible mechanisms of abnormal function.

As discussed above, major depressive disorder is characterised not only by depressed mood, but also by a substantial impairment of cognitive function. Lateral orbitofrontal cortex is activated in healthy individuals undertaking a verbal fluency task. In depressive illness, impaired verbal fluency is associated with attenuated activation in this brain region.[68] During a spatial working memory task done with gradually increasing task difficulty (n-back task), reduction in task accuracy in depressed patients was related to abnormally increased ventromedial prefrontal activity.[69] This relation is consistent with an emotional gating model explaining cognitive performance in depression.[70] Although not specifically described in these studies, increased activity of the ventromedial emotion-related prefrontal region is often associated with underactivity of the cognitive processing region, and vice versa.[71]

Many studies of depressive illness have focused on affective response, though such paradigms always include some cognitive component. Decreased rostro-medial prefrontal and hippocampal activation, and increased temporal lobe activity in depression were shown in a cognitive picture-caption paradigm to generate an affective response.[72] These changes suggest that in depressive illness the decrease in rostro-medial prefrontal and hippocampal activation was associated with impairment of positive affect, and the increase in temporal lobe activity with enhanced negative affect. This anatomical dissociation between positive and negative affective response might be related to abnormality in behavioural reward and inhibition systems proposed on the basis of many studies in animals[62,73] and early deep-brain electrical recording in humans.[74]

A robust finding in neuropsychological studies of depressive illness is a bias towards processing mood-congruent information. By contrast with healthy people, depressed patients show a facilitation of response to stimuli with a negative emotional tone. Studies of abnormal emotional bias have the advantage that they explicitly link mood and cognition in a way that can be related to cognitive-behavioural theories of depressive illness and treatment. In an emotional go/no-go task, patients had attenuated neural responses to emotional targets in the subgenual anterior cingulate and posterior orbitofrontal cortices, and raised responses to sad targets in the rostral anterior cingulate and medial prefrontal cortex.[75] Elliott and colleagues[75] concluded that the orbito-medial prefrontal region has a distinct role in mediating mood-congruent information processing biases in depressive illness. In a study of the neural response to facial expression, a systematic alteration in neuronal activity was associated with such bias in regions that included the parahippocampal gyrus and amygdala.[76] Surguladze and colleagues[76] suggested that this bias could be linked to the negative cognitions and social dysfunction that arise in depressive illness. Depressed individuals characteristically engage in long-term elaborative cognitive processing of emotional information. Using a mathematical, artificial neural network model of attentional biases in depressive illness, Siegle and colleagues[77] made a formal prediction of brain response to positive, negative, and neutral stimuli. They tested these predictions with two emotional processing tasks, and reported that, as predicted, depressed individuals had abnormally sustained amygdala activity in response to affectively negative words, which was related to self-reported rumination.[77]

Formal mathematical models are increasingly used to predict brain activity.[78] Models of emotional learning have been established from extensive work in animals and more recent replicated imaging work on healthy people. Emotional learning involves adaptation and is associated with neural predictive error signals. Mathematical models can describe both the signals and behaviour. The hypothesis that depressive illness is a disorder of emotional learning associated with abnormal error signals was tested with a gambling task.[78] Consistent with the prediction, patients had abnormally increased error signals in various limbic brain regions. The results are consistent with cognitive-behavioural theories of depressive illness, neural plasticity theories of antidepressant action, and successful neurosurgical interventions.[78,79]

The studies[68,69,71,72,75–78] discussed in the previous paragraphs all investigate impaired cognitive function, cognitive-emotional bias and abnormal neural activity in depressive illness. Postulated mechanisms leading to depressive symptoms have been investigated and a focus of the work has been to link clinical presentation with underlying neural activity. Further work in testing these hypotheses in relation to treatment for depressive illness should have priority, since these are the mechanisms of most clinical interest.

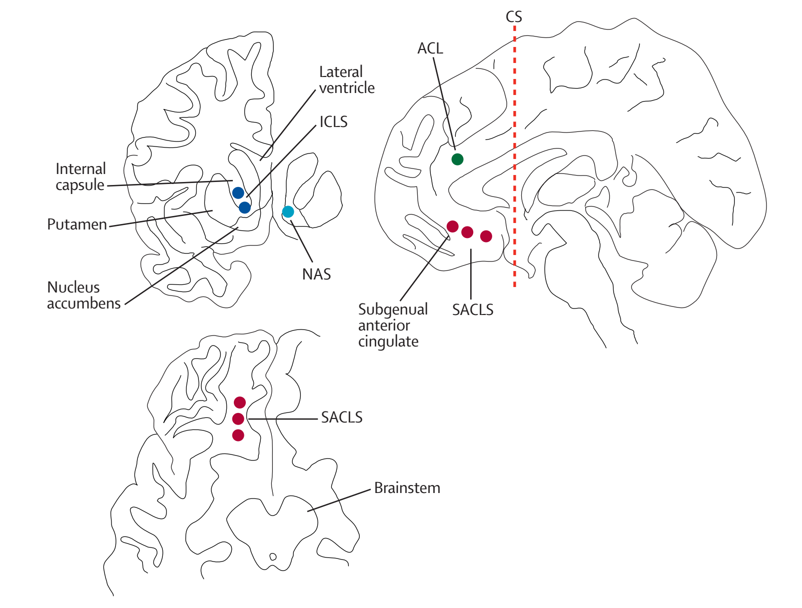

Figure 3: **Deep brain stimulation and lesion sites in the ventromedial prefrontal lobe**
CS=coronal section location, ICLS=internal capsulotomy[187] and stimulation location,[188] SACLS=subgenual and medial orbitofrontal lesion[190] and stimulation[186] location, NAS=shell of nucleus accumbens stimulation location.[189] All interventions were bilateral with the exception of the NAS.[189] For completeness, the supragenual anterior cingulotomy[187] lesion site (ACL) is also shown.

Recent electrophysiological studies of depressive illness might have direct links to quantitative models of brain function. Of particular interest is the error-related negativity (ERN) signal, which is a negative deflection in averaged electroencephalogram (EEG) recordings that peaks about 100 ms after participants make an incorrect response in speeded time-response tasks.[80,81] The onset of this potential precedes the erroneous response, suggesting that the cognitive system knew about the error as it was being made.[81] This signal is sometimes referred to as the response ERN, to distinguish it from another signal, the feedback ERN, which peaks later at 250 ms, and is a response to actual feedback information that the behaviour was incorrect. The neural generators of these signals are in the anterior cingulate,[82,83] a structure repeatedly reported as abnormal in functional and structural neuroimaging studies of depressive illness.[60] The ERN has been suggested to be not only an indication of the registering of an error or conflict, but also of the affective consequences of expectancy violations—in particular aversive emotions including anxiety.[84]

Various experimental studies in healthy participants appear to lend support to these theories. For example, people with high trait anxiety have increased ERN,[80,85] and acute alcohol intoxication decreases the ERN.[86] In clinical studies, patients with obsessive-compulsive disorder who were tested with a speeded reaction-time task showed an ERN with substantially raised amplitude.[87] Gehring and colleagues[87] linked this to abnormal behavioural learning mechanisms and aversive emotional experience. In a more recent study, patients with major depressive disorder undertook a signal detection task with continuous feedback that signalled monetary reward. Compared with controls, patients showed a reduced ERN, and the investigators suggested that this reduction indicated underactivity of central reward pathways.[88] The same group then replicated this finding with a go/no-go task.[89] Since the ERN could arise as a consequence of phasic decreases in activity of the predictive error signals discussed previously,[90] these findings accord with the idea that depressive illness is a disorder of emotional learning.[79]

The link between ERN and aversive emotion lends support to the independent proposal of a direct theoretical link between predictive error signals and polarity and intensity of normal emotion.[91] Although the terms emotion or affect and mood are often used interchangeably in clinical practice, mood is traditionally not emotion, but a sustained predisposition or bias to emotion, expressed as affect, along a single dimension from elation to depression.[92] For a particular emotive stimulus, the abnormal bias associated with a depressive illness should therefore be associated with a corresponding bias of predictive error signals[79] or ERN. Future studies of mood disorder should attempt to clearly distinguish between positive and negative errors of response and feedback, rewarded versus aversive learning paradigms, and unmedicated, acutely medicated, and chronically medicated states. Allelic variation of the serotonergic transporter modulates the ERN.[26] Of equal or more interest are investigations into the effects of acute and chronic administration of antidepressant medication on the ERN and predictive error signals, and the contrast between treatment-responsive and treatment-resistant patients.

The general understanding of depression has evolved from a vague notion of mood and emotion to a differentiated understanding about how emotional and motivational changes interact with information processing in patients' brains. This progress has helped to localise the anatomical structures and neuronal systems underlying depressive symptoms, and at the same time has provided us with a fuller understanding of the real obstacles that depressed patients struggle against.

Treatments

Efficacy of psychological treatments

Cognitive behavioural therapy is a psychological treatment which was first formalised in the late 1970s.[93] The main premise is that depressive symptoms arise from dysfunctional beliefs and thought processes as a result of early learning experiences. These beliefs lie dormant for a number of years, but are activated by a situation or an event that has a specific meaning for the individual.[94] Schema focused work tries to directly address this premise; by definition, a schema is a cognitive structure embedded in long-term memory that has been acquired over a lifetime of learning. At best, this information has been stored to allow a person to perceive and understand. For many patients though, identifying and challenging negative automatic thoughts is the main focus of treatment.

Several studies have shown the advantage of cognitive-behavioural therapy over other psychological therapies and placebo and equivalence to treatment as usual (ie, anti-depressant medication) in the treatment of unipolar depression.[95,96] In a primary care setting, cognitive-behavioural therapy and non-directive counselling were both significantly more effective than usual family doctor care at 4 months' follow-up. However, there was no longer a significant difference between these three treatments at 12 months.[97] Not all research has lent support to the use of cognitive-behavioural therapy over other therapies in the treatment of depression. A study of patients treated with fluoxetine dose increase alone or in combination with cognitive-behavioural therapy examined the frequency of residual depressive symptoms during the continuation phase.[98] The combination of cognitive-behavioural therapy with fluoxetine had equal efficacy to fluoxetine alone. In a further study, pharmacotherapy had an advantage over cognitive-behavioural therapy, which tended to be larger in patients with chronic depression.[99] Research looking at the advantages of combining antidepressants with psychotherapy has been equivocal.[100]

Evidence that cognitive-behavioural therapy reduces rates of relapse and recurrence in unipolar depression has accumulated.[101,102] Although the evidence from these studies is strong, the duration of this preventive effect after the discontinuation of cognitive-behavioural therapy is unclear. In one study the researchers concluded that the effect of cognitive-behavioural therapy in reduction of relapse and recurrence persists for many years, with the effects being lost fully between 3 and 4 years after cessation of the treatment.[103] In a review[104] of the long-term effectiveness of cognitive-behavioural therapy in major depressive disorder Hensley and colleagues concluded that the evidence lends support to the long-term effectiveness of CBT over tricyclic antidepressants alone. This conclusion, however, should be treated tentatively since only five trials between 1981 and 1992 were included. Thus, we need further studies into the prevention of recurrence with cognitive-behavioural therapy.

Klerman and Wiesmann developed interpersonal therapy in the early 1980s,[105] which is based on the premise that depression occurs in a social and interpersonal context. Interpersonal therapy focuses mainly on present rather than past relationships and on interpersonal rather than intra-psychic processes.

Even though the content of interpersonal therapy differs from that of behavioural and cognitive therapies, treatment outcomes for depression are broadly similar.[106] The recently published National (English and Welsh) Institute of Clinical Excellence (NICE) guidelines on the treatment of depression agree with this finding by stating that there is insufficient evidence to determine whether there is a clinically significant difference between psychotherapies such as interpersonal therapy and cognitive-behavioural therapy on reducing depressive symptoms. Furthermore, they suggest that there is some evidence implying that there is no clinically significant difference between interpersonal therapy and antidepressants on reducing depressive symptoms as measured by the Hamilton rating scale for depression.[107]

There is a dearth of systematic reviews and randomised controlled trials (RCTs) on interpersonal therapy in the recurrence and relapse prevention of unipolar depression. However, a sequential treatment strategy in women with recurrent major depression was investigated to look at the efficacy of adding antidepressant medication (imipramine) to interpersonal therapy in those who did not remit with such treatment alone.[108] The study found that in the absence of remission, adding antidepressant pharmacotherapy to interpersonal therapy could be highly effective, enabling a number of individuals to achieve a full remission from depressive symptoms.[108] A similar study was conducted with dysthymic patients in a primary care setting.[109] The findings were similar to the previous study since the researchers showed that interpersonal therapy plus antidepressant medication (sertraline) was effective in reducing symptoms. However, there was no significant difference between sertraline alone and sertraline plus interpersonal therapy, and these two treatment conditions were more effective than interpersonal therapy alone at 6 months' follow-up. This was also the case at 2 years' follow-up.

Additionally, there has been some research on maintenance interpersonal therapy. Maintenance interpersonal therapy employs the same techniques as the standard version, but its main goal is the prevention of recurrence and it is seen more as a long term rather than an acute intervention.[110] The little research that has been compiled on maintenance treatment has concentrated on depression in later life. The findings may be transferable to those suffering with depression between the ages of 18 years to 65 years (mid-life depression). Reynolds and colleagues[111] compared medication (nortriptyline) and interpersonal therapy as maintenance therapies for recurrent depression in older adults. They noted that for the treatment of recurrent depression, medication or IPT were better than placebo and clinic visits in prevention of recurrence. Furthermore, the combination of nortriptyline with IPT was the optimum treatment condition.

Problem solving therapy is a cognitive-behavioural approach. The main goal of the treatment is to alter the problematic nature of the current situation, the patients' reaction to such situations, or to achieve both these goals.[112] It works on the premise that by teaching problem solving skills one is able to improve their ability to cope with life stresses.[113] Problem solving was originally delineated by D'Zurilla and Goldfried[114] and was later revised by D'Zurilla and others.[115] Support for problem solving therapy and the treatment of depression has been fairly strong. In a primary care based study, problem solving therapy was an effective treatment for patients with major depression and the improvement in mood was maintained over a 52 week follow-up.[116] Furthermore, the combination of this treatment with antidepressant medication (paroxetine or fluvoxamine) was no more effective than either treatment alone. In a community study of the prevention of depression, the participants were randomly assigned to either the problem solving therapy or group psychoeducation.[117] Outcomes were positive for both treatment groups at 6 months' follow-up. However, patients that were assigned to problem solving were less likely to report depressive symptoms.

In a study of remission rates and the correlates of remission of minor depression with problem solving therapy in adult and older adult patients, this treatment as well as paroxetine showed greater effectiveness over placebo plus clinical management.[118] Women, younger patients, and those with lower baseline severity of depression were more likely to achieve remission, independent of whether they had been treated with paroxetine, problem solving therapy, or placebo.[119] Furthermore, problem solving therapy seemed less suitable for patients whose minor depression had arisen as a result of more chronic life and health problems.[119]

Thus, problem solving therapy does have fairly strong support for the treatment of depressive disorders. There is, however, a need for further research, since that done has focused mainly on either dysthymia or minor depression and has been done in a primary-care setting. To further enhance the effectiveness of this treatment it would be worthwhile comparing it with other psychological therapies such as cognitive-behavioural therapy and interpersonal therapy.

Although all three treatments seem to be psychotherapies of choice when treating depression, there are other psychotherapies such as behaviour therapy, psychodynamic psychotherapy, and non-directive counselling, to name but a few. However, there are few randomised controlled trials to endorse the efficacy and effectiveness of these treatments in primary care and research settings. An interesting meta-analysis looked at the effects of cognitive-behavioural therapy versus other psychotherapies in the treatment of depression.[120] Psychotherapies were divided into bona fide—ie, those that have been developed with the specific intention of treating depression—and non-bona fide versus CBT. There was no advantage of cognitive-behavioural therapy for depression, and all bona fide psychological treatments were equally effective.[119]

Psychotherapies are now generally recommended as treatment of milder depression or as an adjunct to antidepressant drugs in more severe illness. For obvious reasons their evidence base is thinner than that for antidepressant drugs. There is no evidence for a better rationale of any particular psychotherapy, since several approaches with different underlying assumptions seem to be equally efficacious.

Medication in depression

In a review of antidepressant treatments, NICE went well beyond guidelines published by the American Psychiatric Association[121] by coming to the conclusion that antidepressants are not recommended for the initial treatment of mild depression, because the risk-benefit ratio is poor. Instead it advocates psychosocial treatment or some form of psychotherapy.[107] In moderate to severe depression, antidepressants are recommended, though preferably in combination with psychotherapy.[107] Apart from a small evidence base, there are some practical problems with the implementation of these recommendations, since mood-related cognitive impairment and poor motivation could make psychotherapeutic treatment of depressed patients difficult. Very little evidence exists for the treatment of depression in the context of alcohol and drug dependence, although this is a frequent and important comorbidity. The lack of availability of adequately trained psychotherapists is another obstacle.

The NICE recommendations are representative of a trend in public perception, which seems to run ahead of contemporary clinical practice: Although data on effectiveness have been the prime criterion for deciding on treatment recommendations in the past, risks of side-effects and patients' choice are increasingly taking their place next to treatment effectiveness (see also prescription data for paroxetine in figure 1).[122–124] This change in emphasis explains the NICE recommendation for mild depression, as well as the institution of working groups, and enquiries on the treatment of depression in children and adults by the US Food and Drug Administration, the US Congress,[125] and the UK Medicines and Healthcare products Regulatory Agency.[126] Antidepressant drugs of choice are, in the first instance, serotonin reuptake inhibitors, such as fluoxetine, paroxetine, fluvoxamine, citalopram, and sertraline.[107] The main risks that have been associated with serotonin reuptake inhibitors are treatment-emergent suicidal behaviour and withdrawal symptoms, especially in children and adolescents.[126] Since side-effects are not the primary outcome measure in most drug trials, their recording and reporting tends to be poor. Some potential drug effects, such as suicide, are so rare that drug trials are of necessity underpowered to find any effects. The absence of comprehensive and reliable evidence for risks,[126] perceived industrial interests of clinicians,[127,128] as well as publication bias, which is well known to any author of systematic reviews, have in some quarters eroded public faith in the drug treatment of depression and its regulation.[124,129,130]

The most serious risk associated with depression is increased mortality, especially that due to suicide. Experimental studies of suicide risk or prevention per se are virtually impossible, because of the very low period prevalence of suicide during clinical studies, even in depressed patients. Indirect methods, such as meta-analyses and epidemiological studies provide some lower level evidence.[131,132] Proxy measures of suicide, such as suicidal behaviour, deliberate self harm, or reported suicidal thoughts are more frequent and can be examined instead, as long as they are treated as only one of many risk factors for actual suicide.[133,134] Any intervention that is associated with greater frequency of suicidal thoughts is therefore not necessarily linked to an actual increase in suicides, because suicidal thoughts might in any one case not be the decisive risk factor.[126,133,134] Clinical lore suggests that suicidal risk increases early during treatment, because recovery takes place in degrees, with energy and motivation for example improving before mood. Although there is some evidence of increased suicidal behaviour in the early stages of treatment,[135] this does not seem to be linked to a particular drug or class of antidepressant.[126,133,136] The relative risk of finding serotonin reuptake inhibitors at post mortem after self-poisoning is actually smaller than for other antidepressants, presumably because of their lower toxicity in overdose.[137] Post-hoc studies of patients treated in clinical practice have confirmed that there is no increased risk of suicidal behaviour with serotonin reuptake inhibitors compared with other drugs, despite a potential bias amongst clinicians to prescribe serotonin reuptake inhibitors to suicidal patients, rather than the more toxic alternatives.[135,136,138]

The controversy about serotonin reuptake inhibitor-withdrawal symptoms seems mainly to be about semantics. There is no doubt that withdrawal symptoms occur after stopping SRIs and other antidepressants. The neologism discontinuation symptoms essentially means the same as withdrawal symptoms, without having any association with addiction. Withdrawal symptoms are, of course, a common, but by no means a sufficient criterion to define drug dependence or addiction.[126] Withdrawal symptoms occur particularly, but not exclusively, on withdrawal from paroxetine and venlafaxine. An unexpected and rare symptom is the experience of electric shock sensations, often localised to the head and limbs. With increasing numbers of pregnant mothers going through pregnancy on serotonin reuptake inhibitors, the occasional occurrence of withdrawal in neonates needs to be considered.[139] There is no evidence that antidepressants cause actual addiction.[126]

Drug treatments remain the mainstay of antidepressant therapy. Recent moral panics about suicidal effects and dependence-inducing potential of antidepressants have tilted the balance of publicly perceived risk against them, but both their effectiveness and their ready availability make them the likely choice for most patients.

Physical treatments in depression

Transcranial magnetic stimulation has recently received much publicity, both as an interesting method to investigate neuronal function in vivo in humans and as a potential treatment method to supplement or even to replace drug treatment and electroconvulsive treatment in depression.[140] It has great potential as a non-invasive investigative method, especially if combined with imaging methods. Transcranial magnetic stimulation is able to disturb neuronal activity in a way that allows for the examination of causality, rather than generating associations, as most imaging methods do. Combined with neuroimaging, the spatial distribution of such stimulated neuronal networks can be mapped. After initial enthusiasm about its treatment potential, the current assessment is more sober. The forest plot of controlled trials in depression indicates a secular trend with more recent trials showing smaller effect sizes (figure 2).[140–169]

This pattern might be partly due to the choice of treatment-resistant and drug treated patients, but also to inadequate blinding to placebo. The most commonly used placebo condition is to tilt the coil by 45° away from the scalp, a method that may result in some cortical stimulation or in a different perception of surface stimulation of scalp muscles and skin by the patient. Most studies have focused on high frequency (10–20 Hz) stimulation of the left or low frequency (1 Hz) stimulation of the right dorsolateral prefrontal cortex. There is no good evidence that these are the only coil positions and stimulation frequencies with antidepressant effects, although several neuroimaging studies during such stimulation protocols have shown changes in brain activity and neurotransmitter binding that seem relevant to depressive symptoms.[170–172] The development of new stimulation protocols, such as θ burst stimulation,[173,174] could lead to more effective treatment protocols, but in the meantime transcranial magnetic stimulation remains an experimental treatment modality.

A potential, but rare side-effect of transcranial magnetic stimulation, especially at higher frequencies and intensities, is the induction of seizures.[175] Because of the actual difficulty of inducing seizures reliably with transcranial magnetic stimulation, attempts to replace electric induction of seizures for electroconvulsive therapy (ECT) with this treatment are fairly recent.[176–179] A major advantage of magnetic over electric seizure induction is that the magnetic field can penetrate scalp and skull without hindrance, whereas the electric current used for ECT is impeded by the resistance of surface structures and the brain, requiring the stimulation of various extracranial and intracranial structures before a seizure can be induced. Magnetic seizure therapy is, therefore, likely to lead to less unnecessary stimulation resulting in fewer side-effects such as memory impairment.[176]

Electroconvulsive therapy

Despite public and professional misgivings, ECT remains the most effective treatment for depression, especially if it presents with psychotic symptoms, such as delusions and hallucinations.[180,181] Apart from the risk of general anaesthetic, the main objection to ECT has been its liability to cause memory impairment. Research on cognitive functioning after ECT has been far from comprehensive and is complicated by the improvement of cognition due to the alleviation of depressive symptoms. A recent robust study examined the effects of ECT on episodic memory and noted that the anterograde amnesic effects of ECT were greater for knowledge about the world—ie, impersonal memory, than for autobiographical memory—ie, personal memory.[182] In a systematic review and meta-analysis[180] the UK ECT Review Group stated that data relating to cognitive functioning after ECT were not complete, but the tentative conclusion could be drawn that cognitive impairment consisted mostly of temporary anterograde and retrograde amnesia.[180] Furthermore, the method of ECT used in the treatment of depression was linked to the degree of cognitive impairment produced. For example, bilateral ECT produces greater impairment than unilateral ECT, and higher energy treatment produces greater impairment than lower energy.[183] The effects of ECT are short-lived so patients are likely to require follow-on pharmacological therapy.[184] Further research into the long-term cognitive effects of ECT is recommended as there is a dearth of randomised controlled trials researching this area.[180]

The role of neurosurgery in the management of patients highly resistant to treatment and its invasive nature make future randomised controlled studies unlikely. Vagal nerve stimulation has been proposed as a treatment in drug-resistant and ECT-resistant depressed patients, but the evidence for its effectiveness is as yet inconclusive.[185] Deep brain stimulation as a currently experimental treatment might offer an intervention similar to neurosurgery, which is both reversible and amenable to within-participant placebo control. Six patients with severe refractory depressive disorder, who had failed to respond to antidepressant, psychotherapeutic, and electroconvulsive therapies were treated in an open study, in which electrodes were implanted in the white matter tracts immediately lateral to the subgenual anterior cingulate.[186] Striking and sustained remission of depression was reported in four of the six patients. Furthermore, PET images showed a pronounced reduction in locally abnormally increased subgenual cerebral metabolism, as well as changes in downstream cortical and limbic sites. The authors[186] concluded that disrupting focal pathological activity in the subgenual region using deep brain stimulation could effectively reverse symptoms in depression that is otherwise resistant to treatment.

Other recent studies have reported the results of deep brain stimulation for refractory obsessive-compulsive and anxiety disorders. Based on studies of internal capsulotomy for these disorders,[187] four patients with treatment refractory severe obsessive-compulsive disorder were reported in an open study. The patients had electrodes implanted in the anterior limbs of the internal capsule.[188] This stimulation had beneficial effects in three patients, with one having an especially striking result. For this one patient, the investigators then did a double-blind trial with video assessment and six independent assessors. The findings of the more rigorous double-blind assessment supported the conclusions of the initial less detailed open study assessment; during deep brain stimulation the patient had a pronounced increase in ratings of social contact, communication, flow of ideas, assertiveness and mobility, a decrease in doubt, and no change in sustained attention.[188]

On the basis of this and other work, an open study investigated treatment of refractory obsessive-compulsive disorder and anxiety disorders with deep brain stimulation of the anatomically adjacent shell of the nucleus accumbens.[189] A good reduction in symptom severity was reported in three of four patients. Additionally, PET images of one patient during stimulation showed a change in brain metabolism as a result of the stimulation. Figure 3[187–189] shows the locations of these procedures.

Two distinct issues remain to be determined from such work: treatment effectiveness and treatment mechanism. Determination of treatment effectiveness should take no account of theories of mechanism, but should instead use the accepted methods of evidence-based medicine.[191] The need for evidence-based medicine in assessing neurosurgery for mental disorders has long been recognised. However, there are considerable practical difficulties in implementing evidence-based medicine methods in a treatment of last resort, for which very few patients, even worldwide, are judged suitable. There are no prospective randomised double-blind placebo-controlled trials of any procedure, and none is likely.[192] In the case of deep brain stimulation however, the publication of a double-blind trial[188] in a single patient is encouraging for future studies of stimulation effectiveness.

There are two main theories of treatment mechanism that are not mutually contradictory. Both theories take account of the apparent similarity of clinical response to lesioning and stimulation of the same brain regions. The first theory relates to evidence from work in animals and man for regional specialisation of brain function. In the prefrontal cortex, the ventromedial region seems to be the substrate for normal and pathological emotional experience.[60,62,63,65] Damage to this region in previously healthy people has been reported to diminish emotional experience.[193,194] Deliberate damage to the ventromedial prefrontal region in patients with intractable mood disorder and anxiety might therefore diminish distressing symptoms. Deep brain stimulation at sufficiently high intensities and frequencies has a blocking effect on the stimulated area, mimicking the effects of tissue lesioning.[189] The second theory addresses the issue of whether similar therapeutic effects might occur with limited lesions and weaker stimulation, and has direct links with contemporary stochastic theories of normal brain function. Baev[195] and colleagues have proposed a mechanism of action for partial lesioning and deep brain stimulation in Parkinson's disease. An analogous theory has been proposed for mood and anxiety disorders.[79] Such theories are testable using neuroimaging in people, studies on animals, and quantitative modelling.[79]

Of the physical treatments only ECT is in regular clinical use. Transcranial magnetic stimulation, magnetic seizure therapy and vagal nerve stimulation offer hope of treatment that is potentially less invasive or liable to generate memory impairment. Neurosurgery for mental disorders is reserved for very few highly treatment-resistant patients, whereas deep brain stimulation may be able to emulate some of its effects with the opportunity for blind and randomised assessment, as well as reversibility of its effects.

Summary

Depression is not only a very common, incapacitating, and occasionally lethal illness that deserves our full attention, but also spans a wide range of severity and requires a large choice of treatments. It is common in non-psychiatric medical settings and crucially affects presentation with physical illness and recovery from such illness. All effective treatments for this condition, which is by its very nature associated with the most profound suffering, have to be welcomed.

Conflict of interest statement

We declare that we have no conflict of interest.

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