

Treatment of Depression

The SBU report, "Treatment of Depression", is based on a systematic and critical review of the scientific literature. It is one of a series of scientific reports published by SBU (The Swedish Council on Technology Assessment in Health Care).

The Summary and Conclusions of the report, presented in this booklet, have been approved by the SBU Board of Directors and the Scientific Advisory Committee.

Treatment of Depression

A Systematic Review

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Summary and Conclusions of the SBU Report on: Treatment of Depression

A Systematic Review

March 2004

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Report: Treatment of Depression • Type: A Systematic Review
ISBN: 91-87890-87-9, 91-87890-88-7, 91-87890-94-1
Report no: Three volumes, 166/1+2+3 • Publication year: 2004

Conclusions

- ❑ Treatment of depression should aim at full recovery, i.e., that the patient is not only symptom free but also able to fully function socially and at work. That objective can be achieved for the great majority of patients if available treatment options are consistently exploited (Evidence Grade 1).
- ❑ There are a large number of antidepressants and several types of psychotherapy that have been shown to be effective for treating major depression in adults (Evidence Grade 1).
- ❑ For the acute treatment of mild or moderate depression in adults, several types of psychotherapy are as effective as tricyclic antidepressants (TCAs) (Evidence Grade 1) and probably as effective as selective serotonin reuptake inhibitors (SSRIs) (Evidence Grade 2).
- ❑ Antidepressants and electroconvulsive therapy (ECT) have proven to be most effective for severe depression, such as melancholia and psychotic depression (Evidence Grade 2).
- ❑ Antidepressants and ECT produce more rapid results than psychotherapy (Evidence Grade 2).
- ❑ Maintenance psychotherapy reduces or delays relapses, particularly in cases where acute antidepressant treatment or psychotherapy has not rendered the patient symptom free (Evidence Grade 1).
- ❑ No significant differences have emerged in the effectiveness of various antidepressants for the treatment of mild and moderate depression (Evidence Grade 1).
- ❑ Due to either side-effects or lack of effectiveness, initial antidepressant treatment produces unsatisfactory results in an average of one-third of the patients (Evidence Grade 1).
- ❑ Once antidepressant treatment has resulted in remission, there is a high risk of relapse unless the same dosage is prescribed for at least another 6 months (Evidence Grade 1). Extension of the treatment to 1 year further reduces the risk of relapse.
- ❑ Prophylactic antidepressant treatment for as long as 3 years reduces the risk of recurrence by 50 percent in patients who suffer frequent or particularly severe depressive episodes (Evidence Grade 1).
- ❑ Sudden discontinuation of treatment with SSRIs, or TCAs that affect serotonin uptake, can cause severe withdrawal symptoms (Evidence Grade 2). But these symptoms do not indicate dependence, given that its classic signs – such as a significant dosage increase, preoccupation with tablet intake, or neglect of work, friends and normal interests – are absent.
- ❑ Antidepressants are more effective than psychotherapy for the treatment of chronic low-grade depression (dysthymia) (Evidence Grade 1).
- ❑ ECT is safe and effective, both more rapid and more effective than antidepressant treatment (Evidence Grade 1). But there is a high probability of relapse, and only limited knowledge is available about which antidepressants are effective in preventing relapse (Evidence Grade 2).
- ❑ Transcranial magnetic stimulation (TMS) and vagus nerve stimulation (VNS) are experimental treatments that lack sufficient scientific basis for use in routine medical care.

- ❑ Light therapy has not been shown to be significantly more effective than placebos for treating seasonal affective disorder.
- ❑ St. John's Wort (*hypericum perforatum*) has been shown to be effective for short-term and mild depression (Evidence Grade 2), but its effectiveness in long-term treatment has not been studied. The preparation increases the metabolism of many common medications (including cholesterol lowering drugs, anticoagulants, oral contraceptives and immunosuppressive drugs following organ transplants), as a result of which their effectiveness may be reduced or eliminated.
- ❑ Primary care studies in several countries produced better results than routine medical care when the provider offered patient instruction, telephone support and computerized reminders about treatment protocols, as well as ready access to psychiatrists and psychologists trained in short-term psychotherapy (Evidence Grade 1).
- ❑ One antidepressant, (fluoxetine), has been shown to be effective for short-term treatment of depression in children and adolescents (Evidence Grade 2). No antidepressant has been approved in Sweden for treating that age group.

Controlled long-term trials are completely lacking, though the risk of relapse after short-term treatment is just as high as in adults. There is moderate scientific support for treating depression in children and adolescents with cognitive-behavioral therapy and interpersonal psychotherapy (Evidence Grade 2), but the long-term effectiveness is insufficiently documented.

- ❑ The effectiveness of antidepressant treatment and psychotherapy in the elderly up to the age of 75 is well documented (Evidence Grade 1), but there are no studies of people over 80.

- ❑ Research on effective treatments for bipolar disorder has been very limited, and the results of the numerous trials now under way are not expected for several years. Lithium has been proven to be the most effective drug for the acute treatment of both manic and depressive episodes, as well as for preventive treatment (Evidence Grade 1).

Several new antipsychotic drugs have also been proven to be effective with acute manic episodes (Evidence Grade 1), but there is only moderately strong scientific evidence for their preventive effect (Evidence Grade 2).

Although some drugs originally developed to treat epilepsy are effective with both mania and depression (Evidence Grade 1), only lamotrigine has been shown to have a preventive effect, primarily against depressive episodes (Evidence Grade 1).

- ❑ There are several key areas in which research provides no basis for choosing a particular treatment. Studies are totally lacking when it comes to treating depression in people over 80. There are no studies of antidepressant treatment in children and adolescents that have lasted longer than 10 weeks, and documentation of the long-term effectiveness of psychotherapy in these age groups is very limited.

Principles of Evidence Grading

Evidence Grade 1 (Strong Scientific Evidence) requires at least two well-designed studies characterized by high quality and internal validity. With respect to treatment studies, that means randomized, controlled trials or a systematic, well-designed review of them.

Evidence Grade 2 (Moderately Strong Scientific Evidence) requires one well-designed study characterized by high quality and internal validity, as well as at least two characterized by moderate quality and internal validity (indicating that the study is small or has certain methodological flaws).

A conclusion that no effectiveness has been demonstrated is not assigned any evidence grade, since there may be any number of reasons for such an assessment – the study may have been too small, there may have been major methodological flaws, or no studies may have been performed at all.



SBU Summary

Background

While sorrow, disappointment and temporary mood swings are basic to human nature, pervasive, protracted periods of despondency, feelings of meaninglessness and a sense of hopelessness are typical of depression. In addition, a diagnosis of depression currently requires that the patient's professional or personal life has been affected. But it is difficult to draw a strict line between what is normal and what is pathological, so that a measure of arbitrariness is necessarily involved. Though not unique to psychiatry, the dilemma is particularly evident in this area, given the lack of biological changes so specific to the depressive state that they can contribute to a diagnosis.

The studies on which this report is based employ several different versions of various diagnostic systems. Common to all the systems is that they set criteria for the manner in which diagnoses are to be arrived at or ruled out. There are more similarities than differences among the various systems, but they do not delimit exactly the same groups of people who suffer depressive moods and/or fatigue and loss of interest – the cardinal signs of depression. In addition to a particular diagnostic system, the majority of studies have used one of many scales or interview instruments to specify the severity of the depression. The most common interview instruments are the Hamilton Depression Rating Scale (HDRS) and the Montgomery-Åsberg Depression Rating Scale (MADRS). The Beck Depression Inventory (BDI) is the most frequently used self-assessment instrument. Drug trials normally use the HDRS or MADRS, whereas psychotherapeutic studies tend to employ the BDI.

Depression is among the leading causes of ill health, loss of

productivity and disability worldwide. According to a study published by the World Health Organization (WHO) in 1997, only respiratory infections, diarrhea and infant ailments are greater sources of ill health.

Costs associated with antidepressants, an estimated two-thirds of which were for treatment of depression, totaled some SEK 1.6 billion in Sweden during 2002. Direct costs for doctor's appointments and hospital care were estimated at upwards of SEK 1 billion in 1996. Medical costs for physical illnesses or symptoms related to depression are also high. A large number of studies have demonstrated that depression aggravates many physical illnesses, among the reasons being that such patients tend to lead less healthy lifestyles and are not as likely to comply with treatment recommendations. An attempt to estimate total direct and indirect costs in Sweden for 1997 arrived at a figure of SEK 12 billion.

Many, but not all, studies suggest that depression has become more common in the past 50 years and that onset occurs earlier in life. No scientifically accepted explanation has been presented as yet, but such changes are extremely difficult to account for on the basis of biological factors. Mild and moderate depression represents most of the increase, whereas the incidence of severe depression appears to be constant. However, the reason may be that depression is now diagnosed and treated earlier and consequently does not become more severe.

The box below defines mild, moderate and severe depression in accordance with WHO's *International Statistical Classification of Diseases and Related Health Problems (ICD-10)*. -The categorization employed by the various studies that form the basis of this report to define these levels of severity has normally proceeded from scores on the abovementioned depression rating scales. As a result, the categorization may vary from study to study even when the same terms are employed for various levels of severity.

Diagnostic Criteria

WHO's *International Statistical Classification of Diseases and Related Health Problems (ICD-10)* defines mild, moderate and severe depression, whereas the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* does not clearly explain its corresponding categorization.

ICD-10 requires the following for the diagnosis of a **mild depressive episode**:

- A. Two of the three symptoms – depressed mood, decreased energy and loss of interest or pleasure – have been prevalent during the past two weeks.
- B. No other physical or mental disturbance can provide an explanation.
- C. One of the following symptoms is also present (or at least four symptoms in items A and C):
 1. loss of confidence and self-esteem
 2. abnormal self-reproach or inappropriate guilt
 3. recurrent thoughts of death or suicide, and all types of self-destructive behavior
 4. diminished ability to think or concentrate, or indecisiveness
 5. changes in activity with either slowing or agitation
 6. any type of sleep disturbance
 7. increased or decreased appetite, with associated weight gain or loss

A patient suffering from mild depression is generally disturbed but able to carry on normal activities.

Diagnosis of a **moderate depressive episode** requires the criteria for mild depression, plus at least six symptoms in Items A and C.

A patient in this state is often so affected that even ordinary activities are difficult to perform.

Diagnosis of a **severe depressive episode** requires all three symptoms in Item A and at least five symptoms in Item C.

A patient in such a state is highly dysfunctional, often experiencing abnormal self-reproach and suicidal thoughts, as well as frequent physical symptoms among those described in Item C.

Epidemiology

Most contemporary studies concerning the incidence of depression have been based on a random selection among the adult populations of various countries. While the majority of studies have focused on the 18–60 age group, a few have also included people between 15–18 and up to 65 years. Lay interviewers have been specially trained to employ questionnaires designed to arrive at or rule out psychiatric diagnoses. Such studies have been conducted in countries such as the United States, Great Britain, Canada, Australia and Norway, but not in Sweden. Depending on the wording of the questionnaire and whether Diagnostic and Statistical Manual (DSM) or International Classification of Disease (ICD) – the two major diagnostic criteria systems – are used (as well as possible disparities among the populations of various countries), considerable differences arise.

At any particular time, 4–10 percent of the adult population meets the criteria for a depressive episode. According to studies in Europe, North America and Australia, 5–25 percent of women and 3–10 percent of men suffer at least one depressive episode during their lives. A unique Swedish survey on mental disorders called the Lundby Study was conducted in the late 1940s and repeated 25 years later. Psychiatrists interviewed all 2 500 residents of two communities on the outskirts of Lund in the south of the country. Although that was before international diagnostic systems had been adopted, the study's strength was that experienced psychiatrists conducted it on the basis of criteria that are in close conformity with those currently in use. The study found a much higher incidence of depression than any that had been done earlier. A total of 27 percent of the men and 45 percent of the women would develop some form of depression before the age of 70. The survey correlated more closely with contemporary studies in terms of major depression – 11 percent of the men and 20 percent of the women.

Course of Depression

Most people who have a depressive episode suffer at least one more later in life. Each new episode increases the probability of a subsequent recurrence, and the intervals between them tend to grow shorter and shorter. Psychiatric outpatients suffering from depression who were monitored for more than 10 years experienced depressive symptoms or episodes approximately one-fourth of the time. The few long-term studies that have been carried out on primary care patients indicate a somewhat more favorable course of the illness.

Bipolar patients normally have multiple manic or depressive episodes, the intervals between them also growing shorter and shorter, the more the number of recurrences. Depressive phases are more frequent than manic phases in most patients. The prognosis in terms of social dysfunction, inability to work and premature death is poorer than with unipolar depression.

Gender Differences

With very few exceptions, all studies indicate that the incidence of depression in women is approximately twice that of men. The difference first appears in adolescence, whereas child depression is somewhat more common in boys than in girls. In most studies, the differences between elderly men and women seem to be smaller. The studies covered by this report have included more women than men. No significant differences have been documented between men and women when it comes to the effectiveness of various treatments.

Age Differences

The literature on depression in the elderly is inconclusive. Some studies indicate an equally high incidence as among younger adults, while others suggest a decrease. Many of the disparities

seem to stem from the way in which depression is defined. Depressive episodes in the elderly are often somewhat milder but more protracted. Changes in the aging brain, particularly with co-occurring neurological or cardiovascular disorders, are reflected in a somewhat different pattern of symptoms.

Ethnic and Geographical Differences

Considerable differences have been observed between urban and rural populations, among various European countries, and between the developing and industrialized world with respect to the incidence of depression. The pattern is not unequivocal – high and low incidence has been observed in both the developing and industrialized world. Linguistic and cultural differences in the way that emotions are expressed and interpreted may contribute to some of the disparities.

Social Differences

Poverty and other unfavorable social conditions increase the risk of developing protracted and difficult-to-treat depression.

Mental or Physical Comorbidity

Many people who suffer from depression also have other mental disorders, particularly various kinds of anxiety, substance abuse and personality disorders. The causal relationships are often unclear. Also uncertain is whether limitations inherent to the diagnostic system might not be more responsible for the correlations than the existence of distinct mental disorders. The onset of various anxiety disturbances normally occurs before that of depression.

Depression is common in connection with many chronic physical illnesses. In particular, depressive states often accompany diabetes, cardiovascular disease, multiple sclerosis and other neurological diseases. Depression is a risk factor for more rapid progres-

sion of an illness and for shorter life expectancy. No studies have yet been able to determine whether or not effective treatment of depression improves the prognosis for physical illness.

Project Methodology

In terms of treatment studies, this report includes only randomized, controlled trials, as well as meta-analyses of them. Literature searches were performed in the PubMed, PsychInfo and Cochrane Central Register of Controlled Trials databases. Literature published through the summer of 2003 was included. The manufacturers of drugs examined in the report were contacted about access to unpublished trials, but only a few were obtained in that manner. The report includes publications in the Scandinavian languages, English, German, French, Dutch, Italian and Spanish.

A special quality checklist was used to review the studies. Based on the checklist a global evaluation weighed the reliability of the findings against their applicability to routine medical care.

Although not performing any meta-analyses of its own, the report examined a large number that had been published. The qualitative conclusions in the various sections of the report are not substantially different from the results arrived at by well-designed meta-analyses.

One problem that arose was due to independent releases of the same study having been published without so stating. Careful examination detected a significant number of such studies. Another problem is the tendency to refrain from publishing studies that do not yield the expected findings. Thus, many studies unable to demonstrate the advantages of a particular type of treatment have never been published, as a result of which the effectiveness of the treatment has been overrated.

There are no reliable methods for determining whether unpublished studies exist. For that reason, the authors of this report performed a special examination of treatments for which only a few studies had been published or for which all the studies

had been conducted by the same group of researchers. Psychotherapy appears to be the area in which the greatest risk of systematic errors arises. But it is highly improbable that such errors are of sufficient magnitude as to affect the conclusions drawn by this report.

Unipolar Major Depression

Treatment of Acute Depression with Medication

Assuming that sufficient dosages are prescribed, all drugs that have been approved for treatment of depression are equally effective with its mild and moderate forms. In the case of more severe depression and inpatients, clomipramine and amitriptyline – both of which are TCAs – are somewhat more effective than SSRIs. Early commencement of treatment shortens the length of time that a patient experiences symptoms of depression. Although an improvement in the symptoms may be observable during the first week, several weeks of treatment are generally required before the patient and doctor notice any signs of progress. A couple of months are required to render the patient symptom free, whereas treatment must often proceed for an even longer period of time before he or she is fully able to function socially or at work.

As opposed to their similar effectiveness, the two major classes of antidepressants cause considerably different side-effects. While the TCAs often produce dizziness, fatigue, constipation and xerostomia (dry mouth), the SSRIs more often lead to headaches, nausea and diarrhea. Sexual difficulties are common as the result of SSRI treatment but also occur with the TCAs that affect the serotonin system. In particular, primary care patients with mild and moderate depression tolerate SSRIs better than TCAs. In addition to being discontinued more often, TCA treatment is more likely to result in the prescription of insufficient dosages.

The evidence is still incomplete when it comes to the safety and effectiveness of the other newer antidepressants as compared

to SSRIs. Several studies have demonstrated that venlafaxine is more effective than fluoxetine in terms of the percentage of patient remissions.

Long-term use of most antidepressants, particularly in high dosages, can cause withdrawal symptoms if treatment is terminated suddenly or the dosage is substantially reduced. As a result, such symptoms may arise as soon as the patient has neglected to take the antidepressant for a day or two, and not only when treatment has been discontinued on schedule. Although the withdrawal symptoms may resemble those that initially prompted the treatment, they are often quite different, including severe dizziness, headaches, creeping sensations and general malaise. While only a minority of patients experience withdrawal symptoms, their potential severity suggests that treatment should be phased out over a period of several weeks. Such symptoms do not point to dependence, the classic signs of which – increased dosage, intoxication and socially harmful preoccupation with the drug – are not present.

There is some evidence of a correlation between the concentration of the antidepressant in the blood and clinical effectiveness in the case of nortriptyline, imipramine, clomipramine and – to a certain extent – amitriptyline. Establishing blood concentrations can be useful in determining whether abnormal capacity of the liver to break down the drug may be a cause of severe side-effects with low dosages or lack of effectiveness despite high dosages. Low concentrations may also indicate that the patient is not taking the medication as prescribed.

Most antidepressants compete with other medications for the enzymes that regulate their metabolism in the liver. This competition, which can produce more pronounced side-effects, is a key consideration when prescribing an antidepressant for patients who are already being treated with another kind of drug.

If no improvement is observable within 1 month of treatment and the patient appears to have taken the medication as prescribed, it is unlikely that the treatment will be effective unless a change is

made. There are several alternative strategies for which scientific studies provide some support. Among the options are to increase the dosage to the maximum tolerated by the patient or to switch to another antidepressant. The option of combining two types of antidepressants increases the risk of side-effects and has little support in the research that has been conducted.

Although the most well-documented approach is to increase the antidepressive effect with lithium, it is often viewed as a last resort once all other drug alternatives have failed.

Approximately 1 out of 2 patients who are given a lithium supplement improve, regardless of whether they are suffering from bipolar disorder or not.

Electroconvulsive therapy (ECT) can be effective in patients with therapy-resistant depression, though only about half the time. But it is not known whether the same group of patients improve with ECT as with lithium. Research is still under way on other alternatives in cases where treatment proves to be ineffective.

Once a particular type of antidepressant treatment has rendered the patient symptom free, the risk of relapse is very high unless the same dosage is prescribed for another 6, often 12, months.

Long-term Antidepressant Treatment

Long-term studies indicate that nearly all patients who have received psychiatric care for depression experience recurrent episodes. The risk of relapse is lower for mild depression and primary care patients.

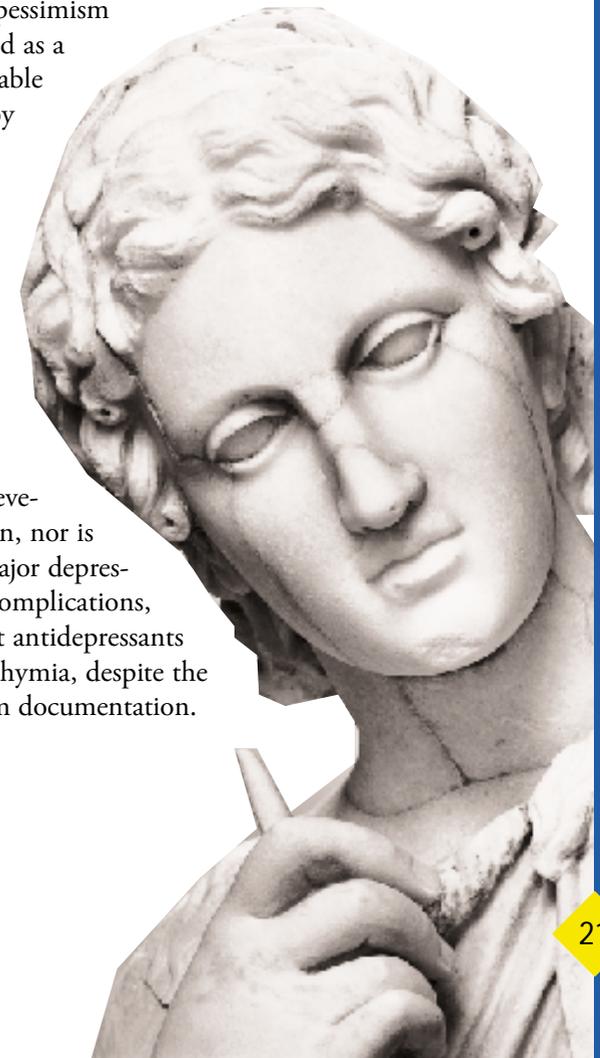
Given that every depressive episode is an ordeal for both the patient and those around him or her, long-term treatment to prevent relapses may be called for. There is extensive evidence that such treatment reduces the risk of recurrent episodes from more than 40 percent to less than 20 percent for up to 3 years. But all of these studies required that their subjects had suffered 2, occa-

sionally 3, depressive episodes during the previous 5 years. It is not known whether preventive treatment is effective in patients whose episodes are less recurrent.

A genetic predisposition for depression, suicide attempts (by either the patient or family members), psychotic symptoms or particularly severe depression may call for prophylactic treatment after the first episode. But comparative studies have not explored this issue, though it is not uncommon clinically.

Chronic Low-grade Depression (Dysthymia)

Chronic despondency and pessimism has traditionally been viewed as a personality disorder untreatable by drugs, though possibly by long-term psychodynamic therapy. Current diagnostic criteria for dysthymia require that a person has been in low spirits for at least 2 years, with only short periods of normal moods, but not to the extent characterized by major depression. However, some dysthymia sufferers develop chronic major depression, nor is it unusual that they have major depressive episodes. Given these complications, there is strong evidence that antidepressants are effective in treating dysthymia, despite the limited amount of long-term documentation.



Treating Depression in People with Physical Illnesses

Most studies of antidepressant treatment have excluded people with serious physical illnesses. But it is very common for depression and physical illness to coexist. Some 60 trials have been conducted on diabetes, cancer, MS, AIDS and stroke patients using TCAs, SSRIs and other antidepressants. The majority of the studies found the drugs to have a significant effect.

Special Types of Depression

ECT is by far the most rapid and effective treatment for severe depression that involves high suicide risk, refusal to eat and drink or psychotic symptoms. Approximately 90 percent of patients with such conditions recover after ECT.

ECT is administered under light anesthesia using a short-acting barbiturate and complete muscle relaxation. Common side-effects are memory impairment, usually temporary, and headaches. Some patients suffer permanent memory lapses for the period during which the treatment was given. But there is no evidence that ECT can result in memory loss for the time prior to the treatment or affect the patient's future ability to learn.

Particularly in countries where the use of ECT is prohibited or highly restricted, studies have been carried out concerning the effectiveness of various drugs for psychotic depression. Antidepressants and antipsychotics are more effective in combination than administered separately. Combination treatment can lead to major side-effects, particularly in the elderly, and has never been compared with ECT.

There is a high risk of relapse after successful ECT. As is the case with acute antidepressant therapy, continuation treatment is required.

No studies have been able to determine what kind of continuation treatment is effective for patients who were given ECT

because antidepressants had proven ineffective. One study on depressed patients who had received ECT for various reasons found that nortriptyline worked better in combination with lithium than by itself. Since the study did not include any group that had received lithium only, it is not known whether such treatment would also have been effective. Though used to some extent, continuation ECT has not been compared with antidepressants or simulated ECT in any study yet published.

Experimental Methods

Subjecting the brain to strong, focused magnetic pulses precipitates activity in arm and leg muscles that can be used to chart various kinds of nerve damage. Researchers observed that transcranial magnetic stimulating (TMS) improved the mental state of neurological patients who were suffering a depressive episode at the same time. A fair number of studies have been conducted on various types of depression, largely to determine whether TMS can be an alternative to ECT but without its short-term impact on memory. The findings have been inconclusive. Since neither the most appropriate part of the brain to be stimulated, the proper strength of the magnetic field nor the number of required treatments has been established, the method must still be regarded as experimental.

The same is true of VNS, during which the pathways to the brain from the left vagus nerve in the neck are stimulated by surgically implanted electrodes attached to a pulse generator in the chest. Several studies are under way but have not been completed. The method is intended for use when all other treatment has failed. But it appears to be less effective if ECT has already been tried without success.

Seasonal Affective Disorder

Certain types of depression occur primarily during the dark time

of the year and often have atypical symptoms, such as a greater need for sleep or craving for sweets. Light therapy has become a standard treatment for that condition. But the trials on which the therapy is based are problematical by virtue of the difficulty in finding a suitable control treatment. Furthermore, no proper evaluation has been performed concerning appropriate dosage and length of treatment. Given that even the weak winter sun exposes the retina to more light than light therapy, a comparison would have been worthwhile. The few published studies comparing light therapy with antidepressants (SSRIs) have not found any differences in effectiveness. That could be due either to the studies having been too small or the antidepressants having lacked any specific effectiveness for this type of condition. A larger study published recently found that one SSRI (sertraline) was significantly more effective than a placebo but made no comparison with light therapy. Studies performed so far have not conclusively demonstrated that light therapy is more effective for depression than placebo.

St. John's Wort

Several extracts of St. John's Wort (*hypericum perforatum*) are available as natural remedies. In some countries, they have been approved as pharmaceuticals and are covered by drug benefits. The active ingredient has not been established, and it has proven difficult to standardize the quantity of herbal substance in the extracts. There is evidence that St. John's Wort is effective with mild and moderate short-term depression. The efficacy appears to be of the same magnitude as conventional antidepressants. The remedy is not effective with deeper or chronic depression. Long-term studies are completely lacking.

Though causing few and only mild side-effects, St. John's Wort can substantially interfere with a series of important drugs (oral contraceptives, cyclosporine, warfarine, simvastatin, nifedi-

pine, anti-HIV agents, theophylline) by acting on the liver enzymes that metabolize them. In addition, St. John's Wort intensifies the action of drugs that affect the serotonin system, in rare cases precipitating a life-threatening serotonergic syndrome. The condition is characterized by confusion, fever and cardiovascular disturbances, which can lead to loss of consciousness and circulatory collapse.

Physical Activity

A number of studies have shown that physical activity elevates the mood of healthy people and those who are in low spirits. Due to methodological flaws in the studies that have tried to demonstrate the effectiveness of various kinds of physical activity on depression, no reliable conclusions can be drawn. Either physical activity has been compared with antidepressants but not with an untreated control group or the various types of exercise (or training) have been compared in individuals or groups. Since behavior modification in different forms constitutes the active mechanism common to various psychotherapies, it may also be at work in physical activity, which often have a social component.

Psychotherapeutic Treatments

The types of treatment that have proven to be effective in depression usually comprise 15–20 hours of individual, couple or group sessions.

Although the focus varies among therapies, they all deal with behavior patterns, cognitive dysfunctions and relationship issues that are linked to depression. Regardless of the theoretical emphasis, treatment is successful only when a patient resumes the activities that were normal or enjoyable before the depressive episode. But whether improvement leads to increased activity or vice versa has not been fully established. Since depression presumably has a number of separate or interacting causes, it is hardly surprising that totally different kinds of therapy can achieve the same results.

But that does not imply that all types of psychotherapy are equivalent – success always requires a focus on the problems that are directly related to depression.

The psychotherapeutic methods for which clinical studies offer the most consistent support are behavioral therapy, cognitive therapy and various combinations of the two. When relationship issues appear to be central, interpersonal psychotherapy and couples therapy have proven effective. A limited number of studies have also demonstrated the effectiveness of short-term therapy based on psychodynamic theory.

A large number of studies on patients suffering from mild or moderate depression have compared antidepressant treatment with cognitive therapy or cognitive-behavioral therapy, while a small number have compared it with interpersonal therapy. Although some early trials used insufficient dosages, that is not true of most later ones. Not a single study has demonstrated that antidepressants are more effective, while several studies favor psychotherapy. But the studies often observe that the effect of antidepressants sets in more rapidly, a dynamic that can be clinically significant. Nevertheless, the two types of treatment produce similar results at the conclusion of the studies.

Attempts to investigate whether severe depression is less responsive to psychotherapy than milder depression have yielded inconclusive findings. The most likely explanation is that this kind of study usually does not recruit patients with severe depression. There is some evidence that depression characterized by disturbed sleep patterns, weight loss, severe anxiety or psychotic symptoms does not usually respond to psychotherapy alone.

A key issue in assessing cost effectiveness is whether successful psychotherapy reduces the risk of new depressive episodes. Earlier studies concluded that the risk of relapse was much less for patients who had been in cognitive therapy than those who had received acute antidepressant treatment. A comparison was made between 15–20 hours of cognitive therapy over a period of 3–4 months (which rendered the patients symptom free) and 1 year of

antidepressant treatment. For the 18 months following conclusion of therapy, there were fewer recurrences than during antidepressant treatment and the subsequent year. In other words, successful cognitive therapy has a protracted preventive effect that antidepressant treatment lacks. That difference is not observable in patients who are monitored for a longer period of time.

As a result of these findings, attempts have been made with various types of maintenance therapy, often monthly sessions. But neither cognitive therapy nor interpersonal psychotherapy has been shown to prevent relapses in patients prone to recurring depressive episodes as effectively as antidepressants.

The risk of relapse is high in patients who improve under antidepressant treatment but do not become completely symptom free. Several studies have shown that supplementing antidepressants with cognitive therapy significantly reduces the risk of relapse – up to 6 years in smaller studies.

Extensive research and methods development is under way in this area, the goal of which is to optimize treatment, identify the active mechanisms involved and determine whether the techniques can be taught to professionals other than those with extensive psychotherapeutic training. Several experimental Internet-based treatment programs have been completed or are in progress.

Identification and Treatment of Patients with Depression in Primary Care

The majority of people with depression are identified and treated outside psychiatric settings, generally in primary care. Primary care physicians also write most of the prescriptions for antidepressants. Only limited data are available on the present treatment of depressed patients in Swedish primary care. Most treatment studies, as well as research on epidemiology and healthcare organization, are from the United States, Great Britain and the Netherlands.

A large number of studies in various countries clearly demon-

strate that more frequent diagnosis of depression does not automatically ensure better treatment or results. Only about half of depression sufferers are generally detected, normally the most severe cases. Simple questionnaires that are either filled out by patients or used by the doctor during an appointment can identify more people with depression. But no studies have shown that this kind of active search is sufficient in itself to improve the quantity or quality of treatment.

Studies that have compared patients who had been identified with those who had not been have failed to find any difference in mental health after 1 year. The explanation may be that the milder types of depression are usually those that go undetected. Many studies with the older generation of antidepressants have indicated that the dosages had been low and the length of treatment too short – and not only in primary care.

Many database studies demonstrate that the use of SSRIs increases the number of patients who are given what appear to be sufficient dosages for a long enough period of time. But a large percentage of patients still receive inadequate care, particularly with regard to the length of their treatment.

A considerable number of studies in the United States have shown that combining doctor and patient training, some form of screening, phone support by a specially trained nurse, computerized reminders about treatment protocols, and access to psychological and

psychiatric consultation improves results for as long as 1 year compared to routine care. But the costs are significant, and it has proven difficult for routine care to incorporate the model into the U.S. system, where nobody is willing to foot the extra bill.

Studies on various models to improve the treatment of people with depression in Swedish primary care are urgently needed to determine whether the kinds of changes described above would lead to better results than the current approach.

Children and Adolescents

Although fairly uncommon in children, the incidence of depression rises rapidly during adolescence, particularly among girls. There is strong evidence for the assertion that adolescents suffer from the same types of depression as adults and are not simply experiencing problems peculiar to their age. Sometimes the most prominent symptoms are acting-out behavior, greater need for sleep and poorer performance in school. But such non-specific symptoms are insufficient in themselves to justify a diagnosis of depression.

There is strong evidence that TCAs are no more effective than placebos in children but slightly more so in adolescents. Antidepressant treatment carries a considerable risk of side-effects in both age groups.

Although there is limited evidence that sertraline and fluoxetine (both SSRIs) are effective in short-term treatment, no studies have lasted for more than 10 weeks despite the likelihood that proper treatment takes 6 months, as with adults. Of the three trials with fluoxetine, the two carried out by the same group of researchers have shown it to be more effective than placebos. The only published study with sertraline suggests that there is very little difference between its effectiveness and that of the placebo. Nonetheless, the size of the study renders the difference statistically significant. Furthermore, the children and adolescents who participated in the study suffered from unusually protracted depressive

episodes and had been recruited from more than 50 treatment centers in a large number of countries on several continents. The centers contributed an average of 8 patients in 2 years, a strong indication that the subjects of the study were not representative of young people with depression.

More studies suggest that cognitive therapy, individual or in a group, is effective as acute treatment. However, the therapy's long-term effectiveness has not been as well documented. Controlled studies of children and adolescents have never compared or combined antidepressants and psychotherapy. Due to reports that there is an increased risk of suicidal thoughts and self-destructive behavior in adolescents who have been given paroxetine and venlafaxine, trials regarding the safety of all antidepressant treatment for children and adolescents are under way in Europe and the United States. The Medicines and Healthcare products Regulatory Agency (MHRA) in Great Britain concluded that efficacy and safety in the treatment of people under 18 had been sufficiently documented only for fluoxetine.

The effects of long-term antidepressant treatment on the developing central nervous system have been insufficiently studied. Long-term studies employing various techniques to map brain structure and function, as well as psychological measurements, are needed before antidepressant treatment of children and adolescents can become routine. Although sertraline and fluvoxamine (both SSRIs) have been approved for the treatment of obsessive-compulsive disorder, even in children and adolescents, specific studies of central nervous system effects are lacking for this group of patients as well.

A few studies have been conducted with children of depressed parents to determine whether psychological counselling and education can prevent or delay onset of the illness. No reliable conclusions can be drawn at this point concerning the effectiveness of such an approach.

The Elderly

Most studies of the elderly have been limited to those under 75, usually sufferers of major depression only. A number of studies have indicated that elderly people tend to exhibit a less pronounced or somewhat different pattern of symptoms that does not fit into the current diagnostic categories. Given these reservations concerning generalizability, a large number of antidepressant studies in the elderly have come up with the same findings as for younger adults. But many studies suggest that it takes longer for a noticeable effect to set in and that the risk of relapse after continuation treatment is greater in the elderly.

There are theoretical grounds for avoiding antidepressants with anticholinergic properties, given that they can impair memory and cause confusion. But comparative studies have not demonstrated such a mechanism to any significant extent, perhaps because these studies did not include particularly old patients. There is insufficient evidence to suggest that antidepressants are effective in treating patients suffering from both depression and dementia. The literature on the effects of psychotherapy is more limited than for younger adults. A great deal of research is presently devoted to adapting various types of psychotherapy to the particular mental and physical losses and changes characteristic of aging.

Bipolar Disorder

Acute Mania

Typical for manic episodes are elevated mood, grandiose plans and flight of ideas, as well as poorer judgement and the absence of boundaries in making new acquaintances, whereas more severe forms of mania include delusions and aggressiveness as well. Mania is also characterized by lack of or limited awareness concerning the abnormal nature of the condition, as a result of which much of the treatment must be carried out against the patient's will.

Newer studies have increasingly recruited patients suffering from milder forms of mania, particularly when a placebo is one of the treatment options. As a result, it is often difficult to generalize study findings to encompass the more severe forms of mania. Severe manic conditions almost always require several types of drugs, often as injections.

A majority of the trials have examined only one drug or permitted supplemental medication to such an extent that it is impossible to determine which one has produced the effect.

The drugs that have been proven to be most effective are lithium, valproate, and neuroleptic agents. Carbamazepine, an older anticonvulsant, has also been shown to be effective with mania. Since the effect of lithium sets in rather slowly, simultaneous acute treatment with neuroleptic agents or benzodiazepines is common. While newer antipsychotics have not been proven to be more effective than the older ones, they are less likely to cause extrapyramidal side-effects.

Both clinical experience and open studies suggest that ECT is effective for severe mania, but only one study has been published comparing it with lithium.

Studies are lacking on the effectiveness of psychotherapy in treating acute mania.

With the exception of lithium, there is little basis in the research for deciding how to structure continuation treatment. Since the treatment prescribed for acute mania is often allowed to go on afterwards, many patients with bipolar disorder are treated with neuroleptic drugs over a long period. Published studies offer no scientific support for that practice.

Treating Depression in Bipolar Patients

Observational studies suggest that antidepressants can trigger acute mania, as well as rapid cycling, i.e., more than three manic or depressive episodes in one year. These studies also identify a greater risk with TCAs than SSRIs.

But it is important to keep in mind that bipolar disorder normally begins with a depressive episode and that not even a comprehensive medical history will always reveal a predisposition to the illness.

Lithium is the treatment that has been proven to be most effective in bipolar depression, and there is evidence that when the patient is already on lithium, a dosage increase can be effective.

If that approach proves inadequate, there is some support for supplementing lithium with an SSRI or with lamotrigine, an anti-convulsant. There is little evidence that valproate, carbamazepine or neuroleptic drugs work for this indication.

Open studies suggest that ECT is effective, though carrying a high risk of triggering a manic episode.

Long-term Treatment of Bipolar Disorder

While the most extensively documented treatment in terms of efficacy, lithium serves primarily to prevent manic episodes. Carbamazepine has a prophylactic effect, though weaker than that of lithium. There is insufficient support for valproate in published studies, and nothing has been published concerning the long-term effectiveness of antipsychotics in bipolar disorder.

Lamotrigine proved effective in two studies that compared it with lithium and placebo, primarily in terms of preventing or delaying new depressive episodes. None of the documented treatments are effective in more than a subgroup of bipolar patients. The drugs are combined in various ways in clinical practice, but no controlled study has been published. While a number of large trials are under way, the findings will not be available for several years.

A handful of well-designed studies have been published recently suggesting that the prophylactic effect of drugs is heightened when supplemented with cognitive therapy or psychoeducational approaches.

A survey among Swedish psychiatric departments concerning the treatment of patients with bipolar disorder revealed that very

few offered more than a specialized lithium clinic. Many drugs for which there was weak evidence of effect were extensively combined. Specific psychological and educational programs for patients and their families were extremely rare.

New Swedish research confirms the greatly increased suicide risk in bipolar disorder.

Thus, both the pharmacological and psychosocial treatment of bipolar patients lacks a sufficient scientific knowledge base and has strikingly inadequate organizational support.

Cost-effectiveness Considerations

A substantial number of studies have compared newer with older and often less expensive antidepressants. A critical review suggests that there is no significant difference in total costs between the old and new drugs. But both observational data and quality of life research suggest that the new antidepressants entail certain advantages. The quality of studies comparing the cost effectiveness of psychotherapy with antidepressant treatment has not been such as to merit any conclusions.

While independent studies suggest that the primary care programs that have been shown to yield better results in the United States are cost-effective, their relevance has been questioned, given that they have not been incorporated into routine treatment due to disagreement about who will cover the higher direct costs.

Research Needs

Despite the extensive literature on unipolar depression, there are large gaps in our knowledge. The individual treatment methods are often insufficient to ensure complete recovery. There is only limited knowledge about the value of switching to a new treatment or combining several treatment modalities. Although prophylactic antidepressant treatment is effective, one out of five patients suffer a relapse within 3 years.

Research on the treatment of children, adolescents and the very old has been highly inadequate.

There is no conclusive evidence about whether successful treatment of depression also improves the condition of patients who are suffering from a physical illness.

The research is insufficient with regard to the most effective treatment for preventing relapses after successful ECT.

The methods and organizational models that yield improved results in primary care depression treatment have never been tried in Sweden.

Sufficient attention has not been devoted to the possible benefits of self-help techniques, such as manual-based or computerized treatment programs.

Controlled studies offer very inadequate support for the current approach to treating bipolar patients in both the manic and depressive phases, as well as for preventive purposes. How the very serious prognosis for bipolar disorder can be improved should be a key area of investigation for both pharmacological and psychosocial researchers.

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- SBU's assessments shall cover the medical aspects and the ethical, social, and economic consequences of disseminating and applying medical and dental technologies.
- SBU's assessments shall be compiled, presented, and disseminated in such a way that all affected parties have access to the information.
- SBU shall contribute, through informational and educational initiatives, toward ensuring that the knowledge gained is used to rationally utilize available resources in health care.
- SBU shall draw on national and international experience and research findings in the field and shall serve as a focal point for health technology assessment in Sweden. This effort shall be managed in a way that secures success and respect for the organization, both domestically and internationally.