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What are the most effective diagnostic and therapeutic strategies for the management of depression in specialist care?

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ABSTRACT

This is a Health Evidence Network (HEN) synthesis report on the most effective diagnostic and therapeutic strategies for the management of depression. There are well documented treatments for depression, mainly pharmaceuticals and psychotherapy.

Collaboration across primary and speciality care including clinician education and nurse case management is of key importance in effective management of depression, enhancing its detection, recognition, diagnosis and treatment. Adherence to evidence-based guidelines improves treatment outcomes. The importance of support in self-management, in particular for elderly people suffering from depression, is well documented in view of the fact that these individuals are particularly underserved.

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Summary

The issue

Depression is a major illness with health and social effects similar to those for chronic diseases like hypertension, congestive heart failure or diabetes. The Global Burden of Disease Programme of WHO indicates that depressive disorders are among the most important causes of death and disability in both developing and industrialized countries. However, there are wide variations in its prevalence and incidence among countries, perhaps partially due to different definitions, diagnostic measures and thresholds. In Western Europe, major depression affects between 5% and 10% of the populations.

Findings

There are several well documented treatments for depression including drugs and psychotherapy. There is also evidence available of effective strategies to improve its management, especially about organizational and educational issues in primary health care. These include the incorporation of clinician education, nurse case management and a greater degree of integration between primary and specialist health care. Some of these strategies have been assessed in the United States, and their applications in Europe might be questionable. The potential benefit of screening for depression is still controversial.

Policy considerations

- There are well documented treatments for depression, mainly pharmaceuticals and psychotherapy.
- Collaboration across primary and speciality care including clinician education and nurse case management is of key importance in effective management of depression, enhancing its detection, recognition, diagnosis and treatment.
- Adherence to evidence-based guidelines improves treatment outcomes. Several established practices and prevailing opinions have been challenged by evidence-based medicine. Many of the recent systematic reviews and studies referred in this document should be consulted for developing guidelines and continued education.
- The importance of support in self-management, in particular for elderly people suffering from depression, is well documented in view of the fact that these individuals are particularly underserved.

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Introduction

Major depression affects about five to ten per cent of the population of Western Europe *(1)*. Most patients with depression consult a primary care physician with non-specific complaints *(2,3)*. Under-recognition and under-treatment are common, despite the relatively high prevalence – about 10% – of major depression according to ICD-10 criteria *(4)* in primary care *(5,6)*. Results of several studies suggest that depression is not recognized in about 50% of people in primary care *(2)* and under-recognition is accompanied by inadequate treatment *(7,8)* (see Figure 1). Depression is a major risk factor for suicide *(9,10)*. There is evidence that almost half of primary care patients with current major depression will at some point develop suicidal ideation *(11)*, often in periods between primary care visits. Primary care providers may be reluctant to inquire about suicidal thoughts out of a belief – unsupported by research findings – that such questions might exacerbate suicidal tendency *(12)*.

The situation in the United States is rather similar to that in Europe. Kessler and colleagues *(13)* reported in their nationally representative survey that the lifetime prevalence for major depression in the United States was 16.2%, and prevalence in the preceding year was 6.6%. Only 21.7% of respondents with major depression in the preceding year reported receiving adequate treatment *(13)*. Furthermore, in the United States, 9.2% of individuals with major depression seek care from a variety of sectors (for example, religious counsellors and social service workers), and 15.3% seek care in the complementary-alternative medicine sector *(14)*. In addition, even when diagnosed, depressed patients have high rates of inadequate treatment and lack of follow-up care, whether primary or specialist *(15,16,17,18,19,20)*, as reported in many countries *(21,22,23)*.

Depression is not only the most frequent mental health problem *(24,25,26)*, it is also a serious illness, responsible for most suicides *(27)*. Moreover, it is increasingly perceived as a chronic disease *(28,29,30,31)*. Thus, it is not surprising that depression causes considerable financial burden to national economies *(32,33,34)*; indirect costs to society have been estimated at seven times the direct costs *(35)*. For example, 57.5 million working days were lost as a result of depression and anxiety in 1987 and 2.5% of the working population reported having depression that limited the work they could

do *(36)*. Thus, depression is a condition with a significant negative impact on the quality of life, daily functioning and productivity. At the same time, there is substantial under-utilization of known efficacious treatments.

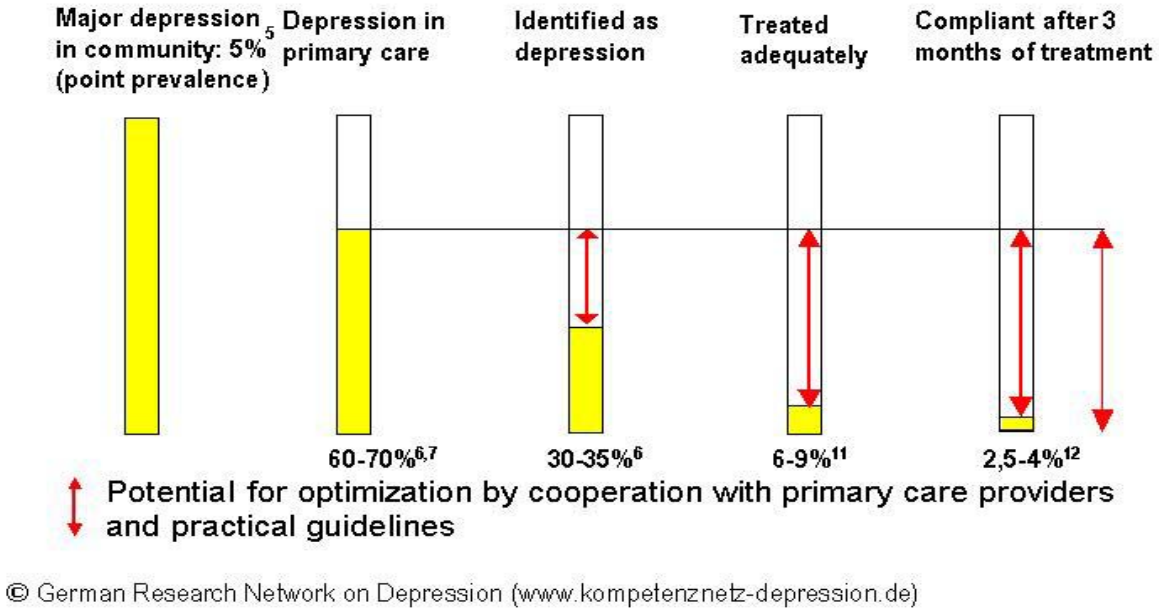

Figure 1. Under-recognition and under-treatment of patients with depressive disorders in primary health care

What is depression?

Depression is commonly viewed as a single disorder, varying primarily in severity. Although classification issues are not in the main focus of the present review there is a need to make clear that there are different types of depression. Standardized diagnostic criteria are used to separate "normal" depressed mood (caused for example by disappointment) from depressive disorders, also referred to as "affective disorders" and "mood disorders". Such criteria are in constant evolution, presently described in the International Classification of Diseases (ICD-10) for the use worldwide *(4)* and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) developed in the United States and dominating psychiatric research *(37)*. Affective disorders are actually syndromes, with only one symptom that is an abnormality of mood (down: depression; up: mania). Clinicians must assess in addition for example, sleep concentration or memory, interest, motivation and somatic symptoms such as headaches and muscle tension If depressive episodes are accompanied by manic episodes, the disease is called bipolar affective disorder in contrast to unipolar affective disorder (only depressive episodes).

Sources for this review

The present review focuses on unipolar non-psychotic depression. The search strategy included use of (a) electronic bibliographic databases (Cochrane Library, PsycInfo and Medline, 1980-2003; main search terms: depression, unipolar and bipolar affective disorder, primary and secondary care, screening, antidepressant treatment, relapse prevention, randomized controlled trials, ECT, psychotherapy) and (b) a few additional studies identified from reference lists. The retrieved studies or reviews were independently read by the authors. Only randomized controlled trials (RCTs) reported in

peer-reviewed journals were considered. The literature research was restricted to studies reported in English. In addition, evidence-based guidelines for depression were considered.

The literature comparing economic evaluations of the full range of treatment options in depression is quite limited. Therefore, few answers related to cost-effectiveness are available. Not only are economic studies rather incomplete, but several issues concerning economic evaluation methodology are unresolved. One important problem is that the unit of cost-effectiveness varies widely between studies (for example, costs per successfully treated case, per avoided admission or per compliant patient), making it very difficult to compare interventions for cost-effectiveness or resource allocation decisions.

Findings from research and other evidence

Recognizing depression

In several countries it has been reported that as many as 50% of depression cases go unrecognized in primary care settings *(2),* for many reasons, including depression's common occurrence in people presenting with physical complaints or symptoms in primary care *(38),* the feared stigma of psychiatric diseases, and the limited time and the competing demands on primary care physicians *(39).* Possible remedies are the routine asking of predetermined questions with high sensitivity and specificity, or use of screening tools with demonstrated high predictive values *(40),* although the utility of the latter is unproved.

Screening

Beyond the high prevalence of depression in primary care, there are other arguments in favour of opportunistic screening for depression, for example:

- There are the well documented impairments associated with untreated depression *(3, 41).*
- Depression in primary care is often associated with somatic co-morbidity and pain, which in themselves negatively affect the recognition of depression *(42).*
- There are under-used but efficacious treatments available *(3,41).*
- Many depressed people in the community and in primary care remain untreated, with a high impact on productivity and economic costs *(41).*
- Depression in the elderly is frequently unrecognized, but there is a good prognosis with recognition and treatment *(43).*
- Screening could be performed with just a few questions from a health practitioner *(44, 45).*

Nevertheless, the problem of false positives can probably not be substantially reduced without increasing missed cases. Several authors have concluded that priority must be given to improving primary depression care before initiating routine screening programmes. This would include a better understanding and management of patients' resistance to the diagnosis, to medication and to therapy *(46,47).*

Whereas cost-utility findings from long-term modelling by Valenstein et al. *(48)* support routine screening programs, randomized trials have suggested that the costs of universal screening outweigh the benefits, except in circumstances where positively screened patients receive immediate strong treatment and careful follow-up *(47).* Furthermore, among other unresolved issues *(49)*, the ideal interval for screening has not been determined *(50,51).* Since there are competing demands on the primary health care physician, the screening instrument needs to be brief and simple, like - for example - the WHO-5 Well-Being Index *(40,52,53).*

Treatment

Depression may be treated by many different pharmaceuticals or psychotherapeutic interventions or a combinations of these. There are many treatment guidelines – differing widely in rigour and evidence-basis – along with recommendations for their quality *(54,55)*. Primary care guidelines partly differ from those for speciality care *(56)*, the choice of treatment varying with the setting. Patients initially seeing a psychiatrist appear to receive more than double the amount of psychotherapy and slightly more pharmacotherapy than patients of other providers *(56)*. In addition, it appears that patients seeing a psychiatrist seem half as likely to have failed treatment compared to patients presenting to a primary care provider (independently of any specific effects of psychotherapy or prescriptions) *(56)*. In light of these findings, achievement of good collaboration across the primary and speciality mental health sectors seems to be crucial, since most patients with depression first seek help in primary care. Consultative roles for mental health specialists have been recommended in support of primary care physicians in the treatment of depression *(57,58)*, but these are American models of uncertain generalizability to Europe.

Moreover, several studies suggest that interventions to improve the quality of primary care depression treatment produce better short-term clinical outcomes relative to usual care, but at increased costs *(7,8,58,59)*. A study of high-utilization patients in primary care found that a quality improvement program was cost-effective relative to usual care, with long-term improvements including physical functioning *(19)*. Less intensive interventions, such as nurse telephone contact, also seem to improve clinical outcomes *(60)*. A recent systematic review emphasized the incorporation of clinician education, nurse case-management and a greater degree of primary and secondary care integration *(61)*. A clinical study *(62)* investigated the cost-effectiveness of "quality improvement interventions" (locally implemented programs that encourage guideline-concordant care for depression) to improve treatment of depression in primary care from a social point of view, suggesting that practice-initiated interventions to improve the quality of care can substantially increase patients' and society's welfare, even when implemented locally and in support of patients' and clinicians' treatment choices. The authors point out that while these interventions increase costs for clinicians and insurers, they did produce gains in patients' labour supply, for example, which on average increased by one additional month of employment over two years *(62)*, making them of particular potential interest to employers and other stake-holders. Other authors have found that most primary care systems in Europe seem to offer inadequate incentives for providers to change practice patterns *(31)*. The results of the study conducted by Schoenbaum et al. *(62)*, might be an argument for changing, if replicated in other studies.

Pharmacological treatment

A large number of studies have demonstrated that antidepressant drugs are effective in treating acute depressive episodes in adults. The goal of acute treatment should always be the complete remission of the episode and not just partial improvement. This goal can be achieved in most patients if available treatments are used appropriately. No matter which is the first treatment chosen, about one-third of patients will either not respond to or not tolerate it. After remission, treatment should be continued for at least six months since the risk of relapse is very high if the treatment duration is shorter. There is also evidence that the same dose effective in acute treatment should be used during the continuation phase.

For many years tricyclic drugs (TCAs, for example, amitriptyline or imipramine) have been considered as references. However, the market also offers heterocyclic drugs, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), as well as newer classes of antidepressants like noradrenergic reuptake inhibitors and those with dual action of serotonin and noradrenergic reuptake inhibition (SNRIs, for example, venlafaxine) *(63,64)*. Thus, it is not always easy to know which drug works best given the efficacy/tolerability profile of a particular patient.

A recent Cochrane review investigating the efficacy and tolerability of amitriptyline compared to other tricyclic/heterocyclics and SSRIs concluded that amitriptyline is at least as efficacious as other tricyclics or newer compounds, but less well tolerated *(65)*. In this meta-analysis, SSRIs show a tolerability advantage over the reference tricyclic drug, in line with clinical experience associating SSRIs with lower rates of fatal poisonings than tricyclics. However, TCAs are still extensively prescribed in some European countries, in contrast to the United States. It is noteworthy that SSRIs cost up to 30 times more than tricyclics, although recent pharmacoeconomic analyses indicate that the categories have similar cost-effectiveness *(66)*. With patents running out, some SSRIs – for example, citalopram – are now as cheap as TCAs.

Tricyclics differ in their side-effects and most randomized controlled trials have compared SSRIs with reference drugs such as imipramine and amitriptyline that are said to have the worst side-effects. Hotopf et al. *(67)* differentiated between old tricyclics (imipramine and amitriptyline), newer tricyclics (nortriptyline, desipramine, clomipramine) and heterocyclics (mianserin, maprotiline), and in comparison, a significant difference between SSRIs and the old tricyclics was found, but none between SSRIs and the newer tricyclics or heterocyclics *(67)*. A more recent systematic review *(68)* assessing the comparative tolerability of SSRIs and the tri- and heterocyclics came to a somewhat different conclusion, showing a statistically significant difference between SSRIs and old as well as newer tricyclics, but again not between SSRIs and heterocyclics *(68)*.

Depressive disorders often complicate recovery from somatic disorders. For example, depression is a risk factor for mortality after acute myocardial infarction *(69)*. Antidepressant treatment with the SSRI sertraline was associated with clinically meaningful improvement of multiple quality-of-life domains in patients with acute coronary syndrome and depression *(70)*. Patients with comorbidities like hypertension or coronary artery disease should use SSRIs (or heterocyclics) because of their lesser side-effects. At the same time physicians must carefully consider potential pharmacokinetic interactions of antidepressants. Patients with suicidal inclinations should receive a less toxic drug in case an overdose is taken. Accordingly, current treatment guidelines such as the WFSBP guidelines *(71)* recommend more recently developed antidepressants such as SSRIs as first choice treatment especially for outpatients in primary care, due to their better tolerability and safety *(71,72)*. On the other hand, clomipramine and to a greater extent amitriptyline have demonstrated superiority in severely depressed inpatients.

Late-life depression often accompanies medical illnesses. Since the elderly are the fastest growing segment of the population in industrialized countries, their health care needs are of special interest. Depressive disorder is sometimes considered a natural consequence of aging and this might be one reason for the under-recognition of depression among the elderly. Elderly depressives run a particular risk of functional decline, hospitalization, and mortality from comorbid conditions and suicide. A number of studies have demonstrated clearly the efficacy and tolerability of antidepressant drugs such as SSRIs (as well as the efficacy of psychotherapeutic interventions) in the elderly *(73)*. Somewhat surprisingly, nortriptyline, a TCA, has been used successfully in many studies, with somewhat poorer tolerability than the SSRIs, but no severe toxicity.

Depression and anxiety frequently occur together. Therefore, adding benzodiazepines to antidepressants is common *(74)*. In a review of 9 studies with a total of 679 patients, the combination therapy group was less likely to drop out *(75)* and more likely to show improvement of depressive symptoms. However, this difference was no longer significant after six to eight weeks *(75)*. The authors warn that the potential benefit of such combinations should be balanced judiciously against possible harm, including dependency, on one hand, and continued suffering in the absence of a response, on the other. Newer antidepressants – several of the SSRIs and dual-action drugs like the SNRI venlafaxine – have been shown to be effective in major depressive disorder and in various anxiety disorders *(76)*. Venlafaxine is best documented for generalized anxiety disorder, while SSRIs have a much better documentation for panic, post-traumatic stress, social anxiety and obsessive-

compulsive disorders. Mirtazapine also appears to be useful in patients with depression who present with predominant anxiety symptoms *(77)*.

Dysthymia is a low-grade but chronic form of depression that lasts for more than two years and is often present in depressed primary care patients. A recent Cochrane review *(78)* concluded that the evidence for the efficacy of TCAs and SSRIs for the treatment of dysthymia were the most robust. This is an important finding since many textbooks and psychiatric authorities still erroneously describe dysthymia as a sort of personality disorder that should primarily be treated with long-term psychotherapy.

Despite the significant prevalence of minor depression (when formal criteria for major depression or dysthymia are not met) in primary care, there is a lack of treatment studies. Five individual studies comparing antidepressant drugs or psychological treatments to placebos in patients with minor depression suggest short-term improvements in symptoms with the SSRI paroxetine as well as with psychotherapeutic approaches *(79)*. In several studies no effect was detected, and in those showing an effect, it was only in females with more severe symptoms. Presently, the category minor depression is not sufficiently deliminated and the evidence for effects is so weak that no evidence-based guidelines for treatment are possible.

Since the mid 1980s, the TCA clomipramine has been recognized as an effective treatment for obsessive-compulsive disorder and is also effective for depressive patients with obsessions and/or compulsions. According to standard definitions in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), obsessions are intrusive, inappropriate thoughts, impulses or images causing marked anxiety and stress. Compulsions, on the other hand, are repetitive behaviours or purposeful mental acts. Patients are often driven to perform their compulsions in response to an obsession. In direct comparisons of clomipramine to SSRIs in obsessive-compulsive disorder with or without accompanying depression, no significant differences in efficacy have been demonstrated, but the tolerability of the former is lesser.

Postnatal depression is a common disorder that can have profound effects on maternal morbidity, the infant and the entire family. A recent Cochrane review found only one trial that met the inclusion/exclusion criteria of the analysis. The SSRI fluoxetine was significantly more effective than a placebo *(80,81)*. After four weeks of treatment, improvement occurred among women receiving fluoxetine after an initial session of counselling, but also after six sessions of cognitive behavioural treatment (see "Psychotherapeutic treatment").

There is an increasing trend towards the use of alternatives to traditional antidepressants, including substances such as *hypericum perforatum L.* (St. John's Wort), the amino acid tryptophan and 5-hydroxy-L-tryptophan (5-HTP; 5-HTP is synthesized from tryptophan). Extracts of hypericum are more effective than placebo for the short-term treatment of patients suffering from mild to moderately severe depressive disorders. However, the current evidence is inadequate to establish whether hypericum is as effective as other antidepressants in these patients *(82)*. Hypericum also interacts substantially with many commonly used drugs, rendering these ineffective and thus should not be used for any patient treated with other drugs *(83)*. Efficacy and safety of tryptophan and 5-hydroxy-L-tryptophan have to be tested in further studies before a widespread use can be recommended *(84)*.

Several studies have emphasized the high rates of relapse (return of symptoms) in depressive disorders *(28,29,30)*. It is therefore important to pay attention to maintenance treatment to prevent both relapse and recurrence (a new episode of depression). It has been proposed that symptomatic improvement occurs before the resolution of the underlying pathophysiology *(20, 28,30,85)*, and remaining symptoms are associated with a high risk of relapse or recurrence. More than two or three depressive episodes indicate that long maintenance treatment is appropriate *(41)*. Despite clear recommendations in guidelines *(86,87,88,89)*, there is still considerable variation in practice, suggesting that many patients with unipolar depression do not receive the optimum long-term antidepressant treatment *(90)*.

In a recent systematic review, continuing antidepressant drug treatment was shown to have approximately halved the absolute risk of depressive relapse, with an average relapse rate of 18%, compared to a placebo's 41% *(91)*. The treatment effect seemed to persist for up to 36 months, although most trials were of 12 months' duration. The evidence of patient outcome from long-term treatment, including optimum length of maintenance needs to be confirmed in further trials *(91)*.

As already indicated above, depression is under-recognized, especially in older people, and is associated with high rates of health care utilization and suicide. Research indicates that SSRIs are also effective in long-term relapse prevention in the elderly *(92)*. Although lithium has been used for some years as the mainstay of maintenance treatment in bipolar affective disorders, the evidence of efficacy in unipolar depressive disorder is less robust *(93)*.

Treatment-resistant depression

Approximately 30% of patients with unipolar major depression experience only partial or no clinical response to the initial antidepressant drug treatment *(94)*. As many as 60–75% of depressive patients suffer from residual or recurrent symptoms *(94)*. There are different tactics for this situation – increasing dosage, switching to another class of drug, augmenting or combining antidepressants – some with strong support from clinical investigations and others based rather on clinical experience *(95,96)*. Augmentation of antidepressants with lithium seems to be a rather well-documented therapy in patients with major depression who do not adequately respond to antidepressants alone *(97,98)*. So-called algorithm strategies are considered useful in overcoming treatment resistance *(99)*.

Electroconvulsive therapy (ECT) is sometimes used to treat severe depressives who do not respond to drug treatment. A recent review and meta-analysis concluded that ECT is probably more effective than drug therapy, though the underlying mechanism is not known. The authors state that "any differences between ECT and drug therapy might not be attributable to the stimulus or shock alone, but could be due to other components of the ECT procedures (including anaesthetic and nursing care)" *(100)*. Only one trial included in the meta-analysis provided data on cognitive functioning: patients treated with ECT had more word recognition errors after treatment compared to patients treated with simulated ECT. At six months this difference was no longer observable. The authors require more evidence for the efficacy of ECT in the subgroups of patients who are presently most likely to receive it: those with treatment-resistant depression and older patients.

Bipolar affective disorder

In patients with bipolar affective disorder a combination of family-focused therapy in combination with pharmacotherapy may improve symptoms and drug adherence *(101)*. The present review focuses on *unipolar* non-psychotic depression. However, from 8 to 20% of patients first presenting with a depressive episode will eventually develop a *bipolar* affective disorder *(102,103)*. For those patients, effective treatment of both depressive and manic episodes is required, along with prophylaxis. More than 90% of individuals who have a manic episode will have additional episodes. The basic pharmacological intervention is the long-term use of mood stabilizers (first choice, lithium) to prevent or reduce the intensity of manic and depressive episodes. The prophylactic efficacy of lithium has been demonstrated in many studies *(104,105)*. There is consistent evidence suggesting that anticonvulsants like valproate and typical and atypical neuroleptics such as olanzapine are effective treatments for acute mania. One RCT in the field found valproate and olanzapine to be equally effective while another found the latter superior *(106,107)*. Anticonvulsants like valproate or carbamazepine or the more recently developed drug lamotrigine are commonly used as adjunctive and alternative mood stabilizing treatments in bipolar affective disorders. Of the three, lamotrigine has the best-documented efficacy, but it mainly prevents depressive episodes. Since the prophylactic effect of lithium is more pronounced for manic episodes, studies of the two drugs in combination are being designed. Despite preventive maintenance treatments, many patients with bipolar disorder still develop depressive episodes. To avoid triggering manic symptoms with the antidepressants and to decrease the cyclic rate of episodes, bipolar treatment often begins with a mood stabilizer. If the patient is already taking one, some authors suggest increasing the dosage as much as tolerable and adding another one.

An antidepressant is recommended if the patient does not respond to this treatment. Thus, there are important differences in the treatment of unipolar and bipolar depression *(108)*.

Gaps in the evidence on pharmacological treatment

A large number of randomized, placebo-controlled trials of antidepressants have been conducted over the past decades, mostly by pharmaceutical companies. It has been recognized that 50% of negative trials go unpublished *(109,110)*, so that results of meta-analyses have to be considered with caution.

Most pharmacological clinical trials exclude the physically ill and elderly depressed patients in phase III trials, contributing to uncertainty about their optimal treatment. However, the Committee for Proprietary Medicinal Products (CPMP) guidelines emphasize the need of phase III studies among the elderly with depression *(111)*. Furthermore, studies are needed of:

- strategies for treatment-resistant depression
- controls for optimal duration of the initial agent
- correlations with neurobiological parameters
- strategies such as switching, augmenting, combining antidepressant drugs
- which patients benefit from which treatment.

All known antidepressants have an onset period of about two to four weeks, so research to improve their onset time is also needed. As mentioned, there is a lack of clinical studies in minor depressive syndromes (not meeting the formal criteria for major depression or dysthymia), although these syndromes are often encountered in primary care and associated with disability, impairment and high economic costs *(112)*.

Psychotherapeutic treatment

A wide range of psychotherapeutic models are available for depression treatment, with differing components. Due to patients' preference for brief interventions *(113)* and to cost *(114)*, the time-limited design has become an important feature of psychotherapeutic interventions. The diversity of psychotherapeutic rationales and techniques is considerable. The main brief psychotherapeutic interventions can be categorized according to their theoretical base into four groups:

- psychodynamic therapy (grounded in psychoanalytic principles)
- interpersonal therapy (IPT)
- supportive counselling (Rogerian person-centred therapy)
- cognitive behavioural therapy (CBT).

Five individual studies comparing antidepressant drugs or psychological treatments to placebos in patients with minor depression suggest short-term improvements in depressive symptoms with problem-solving therapy and cognitive behavioural therapy *(80)*. Moreover, psychotherapy can play a crucial role in addressing special psychosocial contexts and frequent comorbidities such as anxiety disorder *(115)*.

CBT is the most extensively researched psychotherapeutic treatment for non-psychotic unipolar outpatient depressive disorder *(115, 116)*. It developed from cognitive therapy, which focused on dysfunctional beliefs, and then incorporated components of behavioural psychotherapy, and its aim is to correct the negative distorted cognitions and dysfunctional underlying beliefs that maintain depressive symptoms *(117)*.

Most studies suggest that antidepressants and CBT are equally effective in the acute, short-term treatment of outpatients suffering from depression *(118)*. However, the National Institute of Mental Health Treatment of Depression Collaborative Research Program *(119)* concluded that CBT alone is not an effective treatment for *severely* depressed out-patients *(120)*. In contrast, others have concluded from a meta-analysis of four randomized comparative trials that CBT alone can also be considered for the acute treatment of severely non-psychotic depressed out-patients *(118)*. Still others suggest

combining pharmacotherapy and psychotherapy in more severe forms of chronic depression *(121)*. Based on a systematic review of the research, Huibers et al. *(122)* concluded there is good evidence that problem-solving treatment by general practitioners is effective for patients suffering from mild-to-moderate major depressive disorders. The review included CBT, problem solving therapy and counselling as a more "broadly, non-directive approach" *(123)*. There is also evidence that CBT is effective in specific indications such as post-natal depression *(82)* or minor depression *(80)*.

There is evidence that cognitive behavioural therapy reduces relapse rates in patients suffering from major depressive disorders, especially those with residual depression that showed only partial response to antidepressant treatment *(124)*. Although the cost of psychotherapy may exceed that of medication plus usual care in the acute episode treatment *(125)*, it has been suggested that it may be cost-effective if psychotherapy has a durable post-intervention effect. A recent randomized controlled study tested the use of cognitive therapy for relapse prevention in 158 patients with partially remitted major depression despite adequate clinical treatment *(126)*. Cumulative relapse rates in the CBT group were significantly lower than in the control group (29% vs. 47%). The incremental cost incurred for CBT over 17 months was significantly lower than the overall mean costs of CBT *(126)*. However, the limited economic data available suggest that the costs of CBT clearly exceed those of treatment with antidepressants in the acute episode *(125,126)*. A Cochrane review evaluating the evidence for the cost-effectiveness of brief psychological treatments is currently in preparation *(127, 128)*.

Gaps in the evidence on psychotherapeutic treatment

RCTs of psychotherapeutic treatment have been criticized for failing to blind either patients or clinicians and for being tainted by researchers' and therapists' preconceived beliefs *(127)*. In a recent review, Parker et al. *(110)* suggested that "claims for cognitive behaviour therapy's efficacy on depression might have been overestimated" and argued against "viewing cognitive behaviour therapy as a universal rather than a targeted strategy." They argued that, "by testing cognitive behaviour's efficacy in heterogeneous study groups, rather than in specific subgroups, failure to differentiate it from control groups may have been ensured."

At present, evidence suggests that treatment with psychotherapeutic approaches alone in patients suffering from severe major depression is insufficient: a meta-analysis from six controlled studies revealed that psychotherapy alone was effective in milder depression, whereas a highly significant advantage in treating patients suffering from more severe recurrent depressions was obtained through a combination of pharmacological and psychotherapeutic interventions *(129)*.

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