

CONTINUING MEDICAL EDUCATION

Treatment of Depressive Disorders

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SUMMARY

Introduction: A confusing variety of options are available for the treatment of depressive disorders.

Method: Selective literature review under consideration of current guidelines.

Results: The treatment of depression can be divided into acute, maintenance and prophylactic phases. The basic forms of treatment are pharmacotherapy, psychotherapy, and supportive strategies. The approximately 30 antidepressants currently on the market differ mainly with respect to their side effect profiles. Of the specific types of psychotherapy, cognitive behavioral therapy, psychodynamic therapy, and psychoanalysis are funded by the statutory health insurance providers in Germany. All treatment strategies (except for sleep deprivation) show a latency of onset of several weeks and a nonresponse rate of about 30% to 50%. In clinical practice it is essential to follow a stepwise procedure and to perform a standardized evaluation of response after the latency period. In the event of nonresponse, the next step of treatment should be initiated.

Discussion: Depressive disorders have a good prognosis provided one takes best advantage of the available treatment options. Preconditions are continuation of treatment for an appropriate length of time (for antidepressants ca. 4 to 6 weeks, for psychotherapy ca. 4 to 12 weeks) and standardized evaluation of response thereafter.

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The diagnostic evaluation of depressive disorders and their classification as mild, moderate, or severe was presented a short while ago in an earlier issue of *Deutsches Ärzteblatt* (1). If depression has been correctly diagnosed, numerous effective treatment options are currently available. The prognosis of a depressive disorder is good if it is treated appropriately and consistently.

The learning aims of this article are

- knowing the fundamentals of the treatment of depressive disorders (indication, setting, treatment phases, treatment steps)
- learning the principles of establishment of the physician-patient relationship
- acquiring basic knowledge about pharmacotherapy with antidepressants
- acquiring knowledge about treating depression with different forms of psychotherapy.

This continuing medical education article is based on a selective review of the literature, combined with the authors' own extensive experience in the ambulatory and in-hospital treatment of depressed patients. It presents the current state of the therapy of depressive disorders, with an emphasis on treatments that can be provided by general practitioners and family physicians.

Evidence of a depressive episode requiring treatment, as opposed to appropriate grief, can include the following:

- Duration of the depressive syndrome > 2 weeks
- Persistently depressed affect that cannot be lightened even by positive experiences
- A sense of paucity of emotion (the patient does not consider himself or herself to be sad, but rather feels "turned to stone" or "dead within")
- Typical circadian fluctuations, with a morning low and improvement toward evening
- Somatic symptoms without any organic cause

Prognosis

Depressive disorders have a favorable prognosis if the available treatments are applied consistently and thoroughly.

- Inappropriate feelings of guilt, or even depressive delusions
- Suicidality
- Previous episodes of severe depression
- A family history of severe depressive disorders.

The treatment setting

Depression is a very common condition (1). Therefore, its diagnosis and treatment, at least in uncomplicated cases, are tasks not just for the psychiatrist, but for the general practitioner and family physician as well.

- The indications for referral to a psychiatrist are
 - diagnostic uncertainty
 - psychiatric comorbidity (e.g., addiction, dementia, personality disorder)
 - severe depressive manifestations
 - delusional depression
 - depression in the setting of a bipolar affective disorder (bipolar depression)
 - suicidality
 - chronified depression
 - intractability, i.e., nonresponse to one or two treatments that have been carried out appropriately
 - need for psychotherapy or for an intensity of care that cannot be delivered in the setting of a family practice.
- The indications for referral for inpatient psychiatric treatment are
 - acute suicidality or other type of self-endangerment (e.g., refusal of food)
 - severe delusional or other psychotic manifestations
 - depressive stupor
 - the inability, because of illness or other causes, to participate in outpatient treatment on a regular basis (e.g., because of a lack of drive)
 - imminent neglect of oneself because of the lack of an adequately supportive social network
 - external living conditions that would impair the success of outpatient treatment, e.g., severe familial conflicts
 - lack of response to outpatient treatment.

Phases and objectives of treatment

The treatment of depression is divided into three phases (2, 3). The goal of acute therapy is complete or near-complete remission of the depressive manifestations. Because the speed of response of depressive disorders to

treatment varies, acute therapy may need to be given for no more than a few weeks or for many months.

After the acute phase, maintenance therapy is given, with the main goal of preventing an early relapse. Its duration varies from 6 to 12 months. Maintenance therapy is indicated during this period because there is a high chance of relapse regardless of the form of treatment that was used to induce remission in the acute phase (4). In general, the form of treatment that led to remission is continued unchanged into the maintenance phase. A further goal of maintenance therapy is complete functional recovery, i.e., the patient's complete return to his or her premorbid level of function at home, in the workplace, and elsewhere.

Prophylactic therapy is indicated only in patients whose illness has taken a recurrent course, depending on the likelihood of recurrence in the individual case. The latter can best be judged from the number of prior depressive episodes and from the intervals of time between them. If prophylactic therapy is thought to be indicated, it should be started without any temporal endpoint in view (4). This review article will mainly deal with acute therapy.

Principles of treatment

The three main types of treatment for depression are

- pharmacotherapy,
- psychotherapy, and
- supportive measures.

Because of the considerable rate of spontaneous remission, particularly in milder cases of depression (untreated episodes last for an average of 6 to 8 months), the physician and the patient may agree on a two- to four-week period of "watchful waiting" before any treatment is given (5).

The initial treatment of mild or moderate depression should consist of monotherapy, either with a single medication or with psychotherapy, depending on availability and on the patient's preference. In severe, recurrent, or chronified depression, as well as for elderly depressed patients, a primary combination of these two treatment modalities may be advantageous.

Basic treatment strategy

The foundation of any treatment for depression, including but not restricted to specific forms of psychotherapy, is conversation with an empathic and understanding physician in the framework of a stable therapeutic alliance. The patient should sense the physician's acceptance of his or her worries and fears and should feel relieved as a

Depression—a common disorder

The recognition and treatment of depression, at least in cases with an uncomplicated course, is a task not just for psychiatrists, but for general practitioners as well.

The basis of treatment

The treatment of depression is based on conversation with an empathetic and understanding physician and on a stable therapeutic alliance.

result of the therapeutic interview, particularly with respect to feelings of guilt and inadequacy. The physician should inspire optimism by assuring the patient that depression is treatable and has a good prognosis. To this end, it often helps to instruct patients with a biological model of their condition, making it possible for them—particularly in the acute stage—to understand their depressive manifestations as the expression of an illness and thus as a legitimate, temporary dispensation from the duties of everyday life. A biological explanation can often also take away the inexplicable and threatening character of depression. Chronically depressed patients, on the other hand, need stepwise activation and promotion of their individual responsibility and initiative. Over-challenged family members often react with reproaches, trivializations ("everything will be OK soon enough, it's not really so bad"), or exhortations to "pull yourself together." All of these are unhelpful, yet they underscore the necessity of educating the patient's family, too, about depression as a treatable illness and of enlisting them in the effort to bring about recovery. Patients and their families can be motivated to participate in a self-help or family group (see *German Internet addresses listed at the end of this article*). Written patient information can be useful as well (see *Internet addresses*).

A special danger of depressive disorders is suicidality. 3% to 15% of persons suffering from depression commit suicide (e1), while 40% to 70% of suicide victims had suffered from depression (6).

The issue of suicidality should always be addressed repeatedly over the course of treatment. Patients almost always feel relieved when this topic is discussed. For concrete management, see the article by Rudolf et al. (1). Most suicides are announced beforehand in some way, either directly or indirectly.

Important steps to be taken for suicidal patients are the following:

- The immediate commencement of a psychotherapeutic crisis intervention. A stable physician-patient relationship is the most effective protective factor; thus, the family physician plays a central role in such situations.
- Referral to a specialized psychiatrist
- Short-term follow-up at close intervals and clear, unambiguous agreement on the time and place of the next session—no vague offers such as, "give me a call if things are not going well."
- A concrete, 24-hour offer of help: telephone number of the psychiatric crisis service or rescue center

- Obtain the patient's agreement to put off any thoughts of harming himself or herself and have the patient commit to an anti-suicide pact. The latter is an agreement between the physician and the patient in which the patient promises not to harm himself or herself within a specified period of time.
- Inpatient referral or involuntary commitment, if necessary, in accordance with the relevant laws
- For acute suicidality, give benzodiazepine when indicated.

Because there is no single treatment method to which all patients will respond, depression is treated, as a rule, in sequential therapeutic steps (7). The duration of each step should be long enough to give the method used a chance to be effective, yet also short enough to avoid treating the patient ineffectively for any longer than necessary. Four weeks (or six, for elderly patients) has generally been found to be an appropriate period for treatment with antidepressant medications, four to twelve weeks for specific forms of psychotherapy.

At the end of this period, the patient's response to treatment should be evaluated in a standardized fashion. To this end, a detailed documentation of the patient's disease manifestations at the outset of the treatment step is essential. The established, easy-to-use depression severity scales are also helpful—both external assessment scales (e.g., the Hamilton Depression Scale [8]) and self-assessment scales (e.g., the Beck Depression Inventory [9]). A "response" in terms of these scales is generally said to have occurred when the overall score has gone down by at least half during the treatment step in question (10). If this is the case, further treatment should be aimed at a complete remission of the disease manifestations. In case of nonresponse, on the other hand, a transition should be made to the next treatment step.

Pharmacotherapy

Antidepressants

The antidepressants play a central role in the pharmacotherapy of depression. Approximately 30 substances in this class are approved for use in Germany. All are about equally effective (5), with a nonresponder rate of one-third to one-half. All antidepressants have a similar latency until the onset of their therapeutic effect: for practical clinical purposes, a latency of two to four weeks can be assumed (EBM level A [1a]).

Suicidality

A special danger of depressive disorders is suicidality. 3% to 15% of persons suffering from depression commit suicide, while 40% to 70% of suicide victims had suffered from depression.

The treatment of depression

As a rule, depression should be treated in successively applied therapeutic steps, because not all patients respond to every kind of treatment.

With very few exceptions, all available antidepressants work mainly by raising the synaptic concentration of serotonin and/or noradrenaline in the central nervous system. They differ only in the precise mechanism by which they do this (11) (table 1).

Phytotherapy (St. John's wort)

Phytotherapy with St. John's wort preparations is very popular in Germany in particular. The scientific evidence with regard to the efficacy of this agent is mixed at present, with many studies fraught with severe methodological deficiencies. A current meta-analysis (5) comes to the conclusion that St. John's wort is probably effective for the treatment of mild and moderate depression. The more than 40 St. John's wort preparations that are now available on the German market contain extremely variable concentrations of more than 400 individual chemical substances (5).

It is not widely known, yet highly clinically relevant, that St. John's wort carries with it a major risk of interactions with other medications: by inducing isoenzymes of the cytochrome P450 system, it can weaken the effect of many medications, including oral contraceptives, anticoagulants, digoxin, theophylline, other antidepressants, cyclosporine, and anti-HIV agents. Likewise, when a patient stops taking St. John's wort, the serum concentrations of these drugs will rise.

Benzodiazepines

Benzodiazepines have no antidepressant effect in the strict sense of the term, yet they have an acute sedative and anxiolytic effect and their use may thus be indicated for severely depressed and suicidal patients for a period no longer than 14 days. Such treatment is often needed because of the long latency of effect of the antidepressants, which was already mentioned above. The risks and contraindications of the benzodiazepines must, however, be taken into account. For instance, a history of addiction may be a risk that contraindicates benzodiazepine use.

Neuroleptics

Neither the older nor the newer neuroleptics have been shown to be effective as monotherapy for unipolar depression. Neuroleptics are indicated only for the treatment of delusional depression and should only be prescribed by a psychiatrist. Studies have shown that some of the atypical neuroleptics are effective when given in addition to an antidepressant (augmentation therapy), but neuroleptics have not been approved for this indication.

St. John's wort

St. John's wort is likely to be effective for the treatment of mild or moderately severe depression. The available preparations are, however, of variable composition and can lower the effectiveness of many types of concomitantly taken medications.

TABLE 1

The mechanism of action of antidepressants

Mechanism	Pharmacological group
Inhibition of serotonin and/or noradrenaline reuptake	<ul style="list-style-type: none"> ● Tri- and tetracyclic antidepressants (TCA) ● Selective serotonin and noradrenaline reuptake inhibitors (SNRI) ● Selective serotonin reuptake inhibitors (SSRI) ● Selective noradrenaline reuptake inhibitors (reboxetine)
Inhibition of monoamine oxidases	<ul style="list-style-type: none"> ● Reversible monoamine oxidase inhibitors ● Irreversible monoamine oxidase inhibitors
Inhibition of presynaptic autoreceptors	<ul style="list-style-type: none"> ● Presynaptic receptor antagonists

Weekly injections of fluspirilene should not be given because of the risk of tardive dyskinesia.

Lithium

So-called lithium augmentation plays a role in the acute treatment of depression that has not responded to antidepressants (12). Furthermore, lithium as monotherapy is effective for prophylactic treatment in recurrent depression. Treatment with lithium requires special knowledge and precautionary measures and should thus be prescribed only by experienced physicians.

The course of pharmacotherapy

Patient education and shared decision-making

Thorough patient instruction about the effect, duration, and possible side effects of treatment is an integral component of pharmacotherapy. Patients must also be informed that maintenance therapy will be needed after the acute phase of treatment. When discussing these matters with the patient, the physician must address widespread misgivings and ungrounded fears, e.g., of addiction or a change of personality. Patient compliance with psychiatric medication is often inadequate but can be improved by informing the patient about the latency of the antidepressant effect and by describing possible side effects in advance. Shared decision-making (13) means that the well-informed patient should be able to decide for or against taking any proposed antidepressant medication in tandem with the physician. Letting the

Patient education and shared decision-making

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TABLE 2

Antidepressants

Substance group, substances	Initial dose (mg/d)	Standard dose (mg/d)	High dose*1 (mg/d)	Side effect, risk, and interaction profile (selected)	Neurochemical properties
Tricyclic antidepressants: amitriptyline, clomipramine, desipramine, doxepine, imipramine, lofepramine, nortriptyline, trimipramine Tetracyclic antidepressant: maprotiline	25–50	150	300	Anticholinergic effects (dry mouth, constipation, impaired accommodation, urinary retention, delirium, cognitive impairment); orthostatic hypotension; sedation, increased appetite, weight gain (esp. with amitriptyline, doxepine, and trimipramine); heart block, cardiac arrhythmia; potentially lethal toxicity with overdose: beware of accidental (impaired memory) or suicidal overdoses	Inhibition of serotonin and noradrenaline reuptake; also, blockade of muscarinic acetylcholine receptors, histamine ₁ receptors, and α ₁ -adrenergic receptors
MAO inhibitors: Irreversible: tranylcypromine Reversible: moclobemide	10 150	10–30 300–600	80 900	For tranylcypromine, pay close attention to drug information (a low-tyramine diet is necessary—beware of hypertensive crises! Danger of serotonin syndrome when combined with serotonergic medications, or given at too short an interval before or after them!). Side effects: sleep disturbance, orthostatic hypotension, dry mouth.	Tranylcypromine: irreversible MAO-A and MAO-B inhibition; Moclobemide: reversible MAO-A inhibition
SSRI: Citalopram, fluoxetine, paroxetine Escitalopram Fluvoxamine, sertraline	20 10 50	20–40 10–20 50–150	not indicated	Nausea, inner unrest, sleep disturbance, sexual dysfunction, SIADH*2. With fluoxetine, paroxetine, and fluvoxamine, beware of the major risk of interactions with many other drugs because of inhibition of cytochrome P450 isoenzymes!	Selective inhibition of serotonin reuptake
SNRI: Venlafaxine Duloxetine	75 60	150–225 60	375 120	Nausea, inner unrest, sexual dysfunction, rise in blood pressure (esp. venlafaxine), SIADH*2, dry mouth, diaphoresis	Selective inhibition of serotonin and noradrenaline reuptake
Autoreceptor blockers: Mianserine Mirtazapine	30 15	60–120 15–45	180 80	Sedation, increased appetite, weight gain; mianserin: risk of changes in blood count (check periodically!)	Blockade of presynaptic autoreceptors and thus inhibition of negative feedback
Other: Trazodone	50–100	200–400	600	Sedation, sleep disturbance, increased appetite, weight gain, orthostatic hypotension, priapism (inform patient!)	Blockade of serotonin ₂ receptors and presynaptic autoreceptors, moderate inhibition of serotonin reuptake
Bupropion	150	150–300	450	Unrest, sleep disturbance, headache, rise in blood pressure, dry mouth	Inhibition of dopamine and noradrenaline reuptake
Reboxetine	8	8	10	Tachycardia, orthostatic hypotension, inner unrest, sleep disturbance, dry mouth, diaphoresis, urinary retention	Selective inhibition of noradrenaline reuptake

*1High-dose treatment requires more frequent monitoring, sometimes on an inpatient basis, and will predictably result in a higher rate of undesired effects.

*2SIADH, syndrome of inappropriate ADH secretion

patient's family take part in this process also improves compliance.

The choice of antidepressant

The choice of an antidepressant for acute treatment is largely based on the side-effect profile, as the agents used for acute treatment are all comparably effective (table 2). If a particular antidepressant has already been

used effectively to treat a previous episode, then this agent should be preferred.

Sedation is a side effect that may be either undesired or beneficial if the patient suffers from sleep disturbance.

Tricyclic antidepressants should be avoided in a number of situations (5):

- In prostatic hyperplasia, glaucoma, cognitive impairment/dementia, constipation, and co-medication

The choice of antidepressant

The choice of an antidepressant for acute treatment is largely based on the side-effect profile, as the agents used for acute treatment are all comparably effective.

Effectiveness

The effectiveness of antidepressants can only be assessed after they have been given for two to four weeks in standard doses.

with other anticholinergically active substances, because of their anticholinergic side effects;

- In patients with pre-existing heart disease, because they may cause cardiac conduction abnormalities or arrhythmias;
- In suicidal or cognitively impaired patients (risk of deliberate or accidental overdose), because of their greater overdose toxicity compared to other antidepressants.

A reasonable and well-established practice is to give, during the maintenance phase, the same antidepressant that led to remission in the acute phase (4), even though venlafaxine is the only substance officially approved in Germany for maintenance pharmacotherapy. Either antidepressants or, alternatively, lithium can be used for prophylactic therapy in recurrent depression.

Dosing

Each antidepressant has a minimal effective dose; these standard doses are listed in *table 2*, as are the differing starting doses of preparations that must be given initially in a slowly increasing dose. For elderly patients, but for no others, lower than standard doses may already be effective and may, indeed, be indicated because they cause fewer complications. The same antidepressant dose should be prescribed in the maintenance phase of treatment that induced a remission in the acute phase (4). It is very difficult to recommend specific doses for prophylactic treatment at present because of the limited data that are currently available. For prophylactic treatment, too, the standard dose used for acute treatment is probably more effective than a lower dose.

Monitoring

In the first four weeks of acute therapy, the patient should be seen in follow-up at least once a week. At each follow-up appointment, the patient's toleration of the medication should be evaluated, and any concerns on the patient's part should be addressed. The response should be evaluated after four weeks of treatment.

The following tests are recommended for follow-up:

- Before treatment with an antidepressant, complete blood count and transaminases
- If a tricyclic antidepressant (TCA) is used, an ECG as well
- If a TCA or selective serotonin and noradrenaline reuptake inhibitor (SNRI) is used, blood pressure measurement

- Over the course of treatment, repeated complete blood count and transaminases, as well as (in the situations mentioned above) ECG and blood pressure measurement, particularly if the dose is raised
- If selective serotonin reuptake inhibitors (SSRI) are used, then the serum electrolytes should be measured over the course of treatment because of the risk of hyponatremia, particularly in elderly patients.

What to do in case of nonresponse

If the patient's disease manifestations do not respond to treatment with antidepressants in adequate doses for an adequately long trial period, the treatment strategy should be changed. In this situation, a number of options are available.

A reasonable first step consists of measuring the serum concentration of the antidepressant being used. This is called therapeutic drug monitoring (TDM) and is a helpful check on patient compliance as well as a means of detecting any metabolic particularities that may cause an inadequate serum level in the individual patient when taking a standard dose. Blood must be drawn before the medication is taken. For many newer antidepressants, however, there is still no reliably established connection between a therapeutic serum level and a clinical response; thus, TDM is mainly recommended if the agent being used is either a tricyclic antidepressant or venlafaxine. More information on therapeutic levels, the degree of evidence upon which they are based, and the laboratories that measure them can be found on the Internet (*please see list of German-language websites at the end of this article*).

A common strategy after nonresponse to initial antidepressant treatment is to switch to another antidepressant; choosing an agent from another antidepressant class is usually recommended. There is, however, no scientific evidence for the effectiveness of this strategy (14). Thus, the antidepressant should not be changed more than once in the acute phase, and, if the second antidepressant also fails to bring about a response, another strategy should be used.

High-dose antidepressant treatment (*table 2*) is a sensible option for most antidepressants (15). The SSRIs are an exception: these agents have no clear dose-response relationship, so dose escalation of SSRIs lacks a theoretical basis (15). Antidepressants given in high doses can be expected to produce more severe side effects. ECG checks at closer intervals are

For acute therapy

In the first four weeks of acute therapy, the patient should be clinically reassessed at least once per week.

In case of resistance to treatment

- measure the serum concentration of antidepressant
- change the antidepressant (no more than once)
- give the antidepressant in a high dose (exception: SSRI)

obligatory when tricyclic antidepressants are given in high doses; with venlafaxine, the blood pressure must be checked at close intervals. The possible response to high-dose therapy should be evaluated no sooner than about four weeks after it has been initiated because of the known latency until the treatment effect sets in.

A further reasonable treatment strategy after non-response to antidepressant monotherapy is combination therapy with two antidepressants. The effectiveness of combination therapy, however, has only been documented for one specific type of combination, namely that of a reuptake inhibitor (tricyclic antidepressant or SSRI) together with a presynaptic autoreceptor blocker (mirtazapine, mianserin, or trazodone) (16).

Lithium augmentation is the administration of lithium in addition to an antidepressant that has been used hitherto for monotherapy without effect. Adding on lithium can bring about a response in a considerable number of patients, as has been shown in numerous studies and meta-analyses (12).

Psychotherapy

The effectiveness of various forms of psychotherapy in depression has been well documented. Most of the therapeutic effect seems to be due to common, non-specific factors that may also be at work in medical care outside the specifically psychotherapeutic setting. The most important among these factors is a systematically established therapeutic relationship with an accepting, actively listening, and empathetic physician. The physician himself or herself thereby becomes a potent "therapeutic agent," whose importance can scarcely be underestimated.

Most psychotherapeutic approaches to the treatment of depression involve the following strategies:

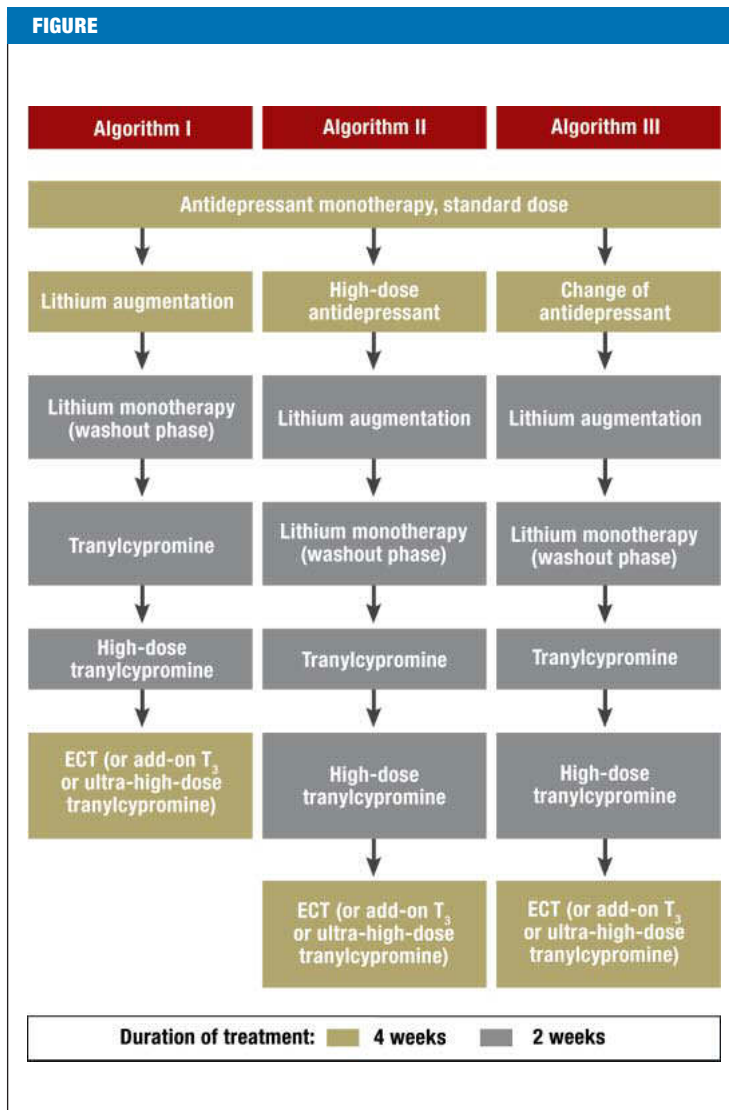
- Resource activation (identification and reinforcement of the patient's current abilities)
- Problem actualization (directed addressing of particular areas of conflict)
- Problem coping (supporting the patient with emotional, cognitive, or active solution strategies)
- Motivational clarification (recognition of problematic modes of perception and behavior and dysfunctional cognitions).

As in pharmacotherapy, patients should be regularly re-evaluated for the possible emergence of side effects, and therapeutic efficacy should be assessed after an adequate period of treatment.

Psychotherapy in the treatment of depression

- Resource activation
- Problem actualization
- Problem coping
- Motivational clarification

FIGURE



Algorithm-based flowchart for stepwise treatment of depression. The flowchart shows the three arms of the algorithm study of the German Competence Network on Depression, because neither the result of the study (supported by the German Federal Ministry of Education and Research) nor the relevant literature permits any definite recommendation to be made. Whether the patient goes on to the next step in any of the three algorithms is a function of the decision procedure. The severity of depression is assessed at the end of each step with the Hamilton Depression Rating Scale (HAM-D, 21-item version).

T₃, triiodothyronine

- HAM-D ≤ 9: remission → clinical reassessment in 2 weeks to confirm remission, if confirmed → transition to maintenance therapy, if not confirmed → next step
- HAM-D decreased by at least 8 points (and overall score > 9): partial response → prolongation of the current step by 2 weeks (no more than once per step)
- HAM-D decreased by less than 8 points: non-response → next step

Algorithm-based stepwise treatment

There are a number of different stepwise algorithms for the treatment of depression. The current state of the data does not permit any definite recommendation to be made.

Specific psychotherapeutic techniques

Psychotherapy for depression can be carried out in an outpatient or inpatient setting, individually or in groups, and with or without the participation of the patient's family. In Germany, the statutory health insurance carriers currently reimburse ambulatory behavioral therapy and deep psychology-based and analytic psychotherapy as so-called guideline techniques.

Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) is based on the assumption that dysfunctional cognitions can lead to disturbed emotions and behavior, and vice versa. A lack of positive reinforcement owing to depression worsens the patient's depressive manifestations. CBT thus involves both cognitive and behavioral approaches. Its treatment strategies aim at overcoming the patient's lack of positive reinforcement, social withdrawal, and conviction of his or her own helplessness. The "cognitive errors" that are often identified among depressed patients include inappropriate generalizations, personalization, emotional thinking, and black-and-white thinking. Etiological importance is also attached to "depressiogenic" cognitive schemata that are learned early on in life and may be reactivated by critical life events; a typical example is the so-called "cognitive triad" of automatic negative assumptions about oneself, the environment, and the future. Cognitive therapy aims to correct these dysfunctional cognitions with structured and directed short-term therapy consisting of an average of 20 sessions. The efficacy of ambulatory CBT against depression has been very well studied and has also been confirmed by meta-analyses (17, e2–e4).

Deep psychology-based and psychoanalytic psychotherapy

Classical psychoanalytic treatment is performed with the patient lying on a couch, several times weekly, over a long period of time. Deep psychology-based psychotherapy is based on central fundamental assumptions and principles of psychoanalysis, but it is usually performed with the patient sitting in a chair, only once per week, and over a shorter period of time. Both of these types of psychotherapy are based on the assumption that depressive disorders are largely due to unconscious processes whose roots typically lie in the patient's childhood. Depressed persons, in particular, often suffer from uncertainties in their relationships and a negative bonding style with increased vulnerability to losses and affronts. More than in other types of psychotherapy, the therapist-

patient relationship itself becomes an object of treatment, because the patient's typical relationship pattern and anxieties are reproduced in this relationship and can be addressed within it.

The currently available data from controlled studies of efficacy are less extensive than for CBT. More structured, short-term deep psychological psychotherapy in mildly or moderately depressed patients has been the type most frequently studied (e5). Other studies and meta-analyses have involved patients with a mixture of diagnoses, so that it is difficult to draw any specific conclusions about the effectiveness of these types of treatment for depression (e6, 18).

Interpersonal psychotherapy (IPT)

IPT is a type of short-term psychotherapy that was developed specifically for the treatment of depression. It consists of 12 to 20 hours of semi-structured psychotherapy, generally in weekly sessions, and focuses on the psychosocial and interpersonal aspects of depressive disorders. Thus, it places particular emphasis on coping with grief, role switching, life changes, and interpersonal conflicts.

Although much evidence for the efficacy of IPT is available from controlled studies and meta-analyses (19), in which it was used alone or in combination with antidepressants, IPT is currently not reimbursed by the statutory health insurance carriers in Germany.

Supportive measures

The importance of involving the patient's family has already been mentioned more than once. The only treatment for depression that has an immediate therapeutic effect is sleep deprivation, which can be done on an inpatient or outpatient basis. The patient is required either to do without sleep for an entire night (complete sleep withdrawal) or simply to get up between 1 a.m. and 2 a.m. (partial sleep deprivation), without making up for the missed sleep either in advance or afterward. It is crucial for the success of this treatment that the patient should not take even a short nap during periods of wakefulness. About 60% of patients so treated have a marked improvement of mood the day after.

The main disadvantage of sleep deprivation treatment is that its beneficial effect lasts no more than 1 or 2 days in about 80% of patients. If the treatment is effective, it can be repeated once every 3 to 4 days. An absolute contraindication is a history of epileptic seizures; relative

Cognitive behavioral therapy

The effectiveness of cognitive behavioral therapy in the outpatient setting has been very well studied and has also been confirmed by meta-analyses.

Supportive measures

Roughly 60% of patients undergoing sleep withdrawal therapy experience a marked improvement of mood for 1 to 2 days thereafter.

contraindications include bipolar or psychotic forms of depression.

The effectiveness of light therapy with special apparatus has been unequivocally documented only for seasonal depression (winter depression) (e7). Physical activity probably has a beneficial effect on the resolution of depression and can be recommended as a supplementary treatment, even though the scientific data to support this are as yet inadequate (e8). Treatments that are currently under investigation include aerobic training and endurance training (treadmill running) (20).

The most effective of all treatments for depression is probably electroconvulsive therapy (ECT), for which the current main indication is treatment-resistant depression (21, 22). Because of the specialized personnel and apparatus that this form of treatment requires, and also because of persistent, widespread misgivings about it, ECT is used only when multiple previous therapeutic attempts have failed, or when the patient explicitly requests it. Its beneficial effect typically appears after one to three weeks of treatment with three ECT sessions per week. Its major clinical drawback is the high rate of early recurrences in the first 16 weeks—up to 75% of patients who are not subjected to continuing treatment. With good maintenance therapy, the percentage of early recurrences can be reduced to about 35%, but such recurrences cannot be eliminated.

Conclusion

Depression can be treated effectively at present because multiple forms of treatment are available that complement each other or can be given in combination. Most of them have been well documented as effective in properly designed, controlled studies. No single form of treatment can be considered superior to all of the others, and a relatively high nonresponder rate is a common feature of all of them. Thus, the art of treating depression consists of a methodical and exhaustive use of the available therapeutic options within the framework of an algorithm-based stepwise treatment regimen (*figure*), in which each sequential step of treatment is carried out for an adequate length of time and is then evaluated for effectiveness in standardized fashion. Randomized comparative studies have shown that stepwise treatment leads to more frequent and more rapid treatment responses than unstructured treatment, while simultaneously reducing the amount of psychoactive medication that must be prescribed as well as the frequency of changes in treatment strategy (7).

High nonresponder rate

The treatment of depression must make thorough use of all of the currently available therapeutic options in accordance with a stepwise treatment algorithm.

Conflict of interest statement

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For e-references please see:
www.aerzteblatt-international.de/ref4508

For a case illustration relating to this article,
 see the following website:
www.aerzteblatt-international.de/0812

German-language websites for further information:

- Self-help and family groups:
www.nakos.de
- Written information for patients:
www.akdae.de/45/Depression.pdf
www.kompetenznetz-depression.de
- Information about therapeutic serum levels of antidepressants and grades of supportive evidence:
www.agnp.de → Arbeitsgruppen → AG Therapeutisches Drug-Monitoring

Further Information

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1/c, 2/d, 4/c, 5/b, 7/d, 8/c, 9/c, 10/e. All answers to questions 3 and 6 were counted as correct.

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

What is the objective of maintenance therapy for depressive disorders?

- (a) Phase prophylaxis
- (b) Remission
- (c) Response
- (d) Relief of symptoms
- (e) The prevention of an early relapse

Question 2

In what respect do the roughly 30 antidepressants that are currently available in Germany differ from one another most markedly?

- (a) Their side-effect profiles
- (b) Their nonresponder rates
- (c) Their addictive potential
- (d) Their latency of onset
- (e) Their potency

Question 3

A 68-year-old woman in whom you have diagnosed moderately severe depression will only accept St. John's wort as the sole pharmacotherapeutic agent against depression. What should be your particular concern if you prescribe her a preparation containing this substance?

- (a) The potential for morbid obesity
- (b) The ECG
- (c) Any medications she is concomitantly taking
- (d) Renal function
- (e) Possible addiction

Question 4

A 59-year-old bus driver presents to you with a history of depression that began two months ago. You are considering treatment with a tricyclic antidepressant. Which of the following comorbidities would lead you not to prescribe a drug of this type?

- (a) Bronchial asthma
- (b) Gout
- (c) Prostatic hyperplasia
- (d) Psoriasis
- (e) Rheumatoid arthritis

Question 5

What is the most rapidly acting treatment for depression?

- (a) Depression-specific psychotherapy
- (b) Electroconvulsive therapy (ECT)
- (c) Light therapy
- (d) Pharmacotherapy with antidepressants
- (e) Sleep deprivation

Question 6

According to the theory underlying psychotherapy based on deep psychology, what psychological phenomenon is more common in depressed people?

- (a) Borderline personality structure
- (b) Latent homosexuality in a parent

- (c) Penis envy
- (d) Increased vulnerability to loss
- (e) Documented above-average intelligence

Question 7

Which of the following antidepressive treatments has been well documented to be effective by multiple controlled studies and meta-analyses?

- (a) Physical activity
- (b) Neuroleptic monotherapy
- (c) High-dose SSRI treatment
- (d) Outpatient cognitive behavioral therapy
- (e) Changing the antidepressant in case of nonresponse

Question 8

What is meant by an algorithm-based stepwise treatment regimen for depression?

- (a) Alternation between psycho- and pharmacotherapeutic techniques until a remission occurs
- (b) Choice of treatment according to the classification of the patient's depression as mild, moderate, or severe, on the basis of a systematic evaluation
- (c) Treatment of depression with monotherapy or with a combination of two, three, or four therapeutic methods, depending on the systematically assessed degree of resistance to treatment
- (d) Determination of the treatment plan with the aid of treatment software that processes the data of the individual patient on the basis of a response probability matrix
- (e) Determination of a multi-step treatment plan at the beginning of treatment with a standardized response evaluation at the end of each step, whose results determine the transition to the next treatment step

Question 9

Which of the following is a basic assumption of cognitive behavioral therapy?

- (a) Placing the overwhelming emphasis on cognition, rather than emotion, is a central element in the pathogenesis of depression.
- (b) Depressive disorders are based to a large extent on unconscious processes.
- (c) Dysfunctional cognitions lead to disturbed emotions and behavior.
- (d) Cognitive ego-splitting lies at the heart of depressive disorders.
- (e) Excessive positive reinforcement in the consumer society is the main cause of depression.

Question 10

What tests are advisable before the beginning of treatment for depression and regularly over the course of treatment?

- (a) Stress ECG for sertraline treatment
- (b) Blood pressure checks for venlafaxine treatment
- (c) EEG for citalopram treatment
- (d) Metabolizer status checks for amitriptyline treatment
- (e) Serum level determinations for treatment with reboxetine

CONTINUING MEDICAL EDUCATION

Treatment of Depressive Disorders

Tom Bschor, Mazda Adli

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CONTINUING MEDICAL EDUCATION

Treatment of Depressive Disorders

Tom Bschor, Mazda Adli

Case

Treatment of Depressive Disorders

A 46-year-old office worker went to his family physician, accompanied by his wife, complaining of persistent headaches. When questioned more closely, he described a dull pressure in the entire head that had been present continuously, though at varying intensity, for approximately the past four weeks. His chronic back pain had worsened in the same period. Because of these problems, he had first stopped attending his weekly chess night and then stopped going on his usual weekend excursions with his family. Over the course of time, he had stopped performing any tasks at all for his family and household. He had stayed home from work for the past three days. A thorough physical examination revealed no abnormality.

Only on directed questioning did the patient state that he had felt exhausted and bereft of energy all the time for the past few weeks, that he had lost interest in his usual activities, and that he no longer enjoyed the things that used to give him pleasure. His food no longer tasted good to him, and he had already lost 2.5 kg of weight. Most recently, he had begun to have difficulty falling asleep and to wake up every morning between 4 and 5 a.m.; he attributed this to the headaches. His wife, on directed questioning, said that her husband often seemed sad and that she had seen tears in his eyes for no apparent reason on multiple occasions. Nor could she understand why her husband, who was normally very conscientious about his work,

now continually worried about the possible implications of his current three-day absence for his job security and the family's financial future.

The addiction history and past psychiatric history were negative. There was, however, a positive family history: the patient's paternal grandfather had committed suicide, for unknown reasons.

The family physician diagnosed a first depressive episode, informed the patient and his wife of her diagnosis in two separate interviews, and stressed both the nature of the symptoms as a disease and the good prognosis for recovery.

She declared him unable to work for two weeks and urged him to take a one- to two-hour walk each morning, but to take on no further tasks or activities. The patient was able to accept the temporary, passive role of an ill person only when acute depression was explained to him through an analogy to acute pneumonia. The patient and his family physician agreed that he would take antidepressive medication; she prescribed nortriptyline (150 mg/day), an agent with both serotonergic and noradrenergic properties, because such agents can be expected to have an additional beneficial effect in pain. Other than dry mouth, the medication was well tolerated. The patient and his family physician saw each other weekly. Three weeks after the onset of treatment, the patient came for the first time without his wife accompanying him and reported that he had just begun working in the garden again on his own initiative. After a total of five weeks of treatment, he was practically free of symptoms and returned to work. The patient and his family physician agreed that he would continue taking nortriptyline for six months as maintenance therapy.