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Unipolar Depression

Short version

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The long version of the guideline was finalized on October 08, 2009. It is intended to revise and re-publish the guideline every 4 years, measured from the time period of publication. The German Society for Psychiatry, Psychotherapy, and Neurology (DGPPN) is responsible for continuously maintaining, updating, and disclosing the S3-Guideline. The Agency for Quality in Medicine (ÄZQ) and the Guideline Commission of the Association of the Scientific Medical Societies (AWMF) are responsible for the National Disease Management Guideline.

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- **Version 1.3, January 2012:** Version renumbering according to the long version
- **Version 1.2, August 2011:** First published version, numeration in accordance with the long version

VERSIONS OF THE GUIDELINE

The published S3-Guideline/NVL Unipolar Depression includes the following components:

- I. A short version explaining the basic care features and graduated recommendations (**the present document**);
- II. A long version containing background explanations on the evidence and a list of references in addition to the content of the short version;
- III. S3/NVL-Guideline Report;
- IV. NVL-Patient Guideline;
- V. NVL-Practice Guide, eg, where required, abbreviated information for medical staff/ pocket versions for the physician.

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Because medical sciences are subject to constant change, any information, especially on diagnostic and therapeutic procedures, only reflects the knowledge at the time of the print of the Clinical Practice Guideline. The enclosed recommendations on the therapy, choice and dosing of drugs were drafted with greatest possible care. Nevertheless, the users are encouraged to use the package leaflet and specialized information as a reference and consult a specialist in case of doubt. In the general interest, the users are asked to inform the NVL-Editorial Office about debatable discrepancies.

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1 Goals and Purpose of the Guideline

Depressive disorders are among the most common diseases and most common reasons for medical consultation in health care. Although the research into treatment options has advanced considerably in the past years, there is room for improvement in all the areas of care for patients with depression, especially in the graduated and integrated care between family, specialist, and psychotherapeutic treatment, as well as in the decision on indications for outpatient- and inpatient treatment methods and their coordination. It is not uncommon for the treating practitioner and the patients to have preconceptions against evidence-based treatments, eg, pharmaco- or psychotherapy, which make a satisfactory treatment difficult.

The goals of the guideline are

- to improve the identification, diagnostics and treatment of depression in Germany;
- to draft, coordinate, and implement key recommendations on pressing health care problems between the teams of care providers including patient- and family representatives;
- to state and update the recommendations according to the latest research, taking into account the principles of evidence-based medicine;
- to enable the effective distribution and implementation of the recommendations through reaching a consensus among all the involved disciplines, organizations and patients.
- to show the treatment flows for depressive disorders across the various areas, to indicate decisive situations and to define the optimal approach;
- to give specific recommendations on the choice and coordination of care by all involved specialist disciplines and other specialized professions in health care;
- to identify the specific characteristics of the German health care system and draft the process recommendations accordingly, taking into account the international literature;
- to identify barriers to implementation of the guideline recommendations and show solutions;
- to work towards the systematic implementation of the program recommendations in education, training and quality management systems.

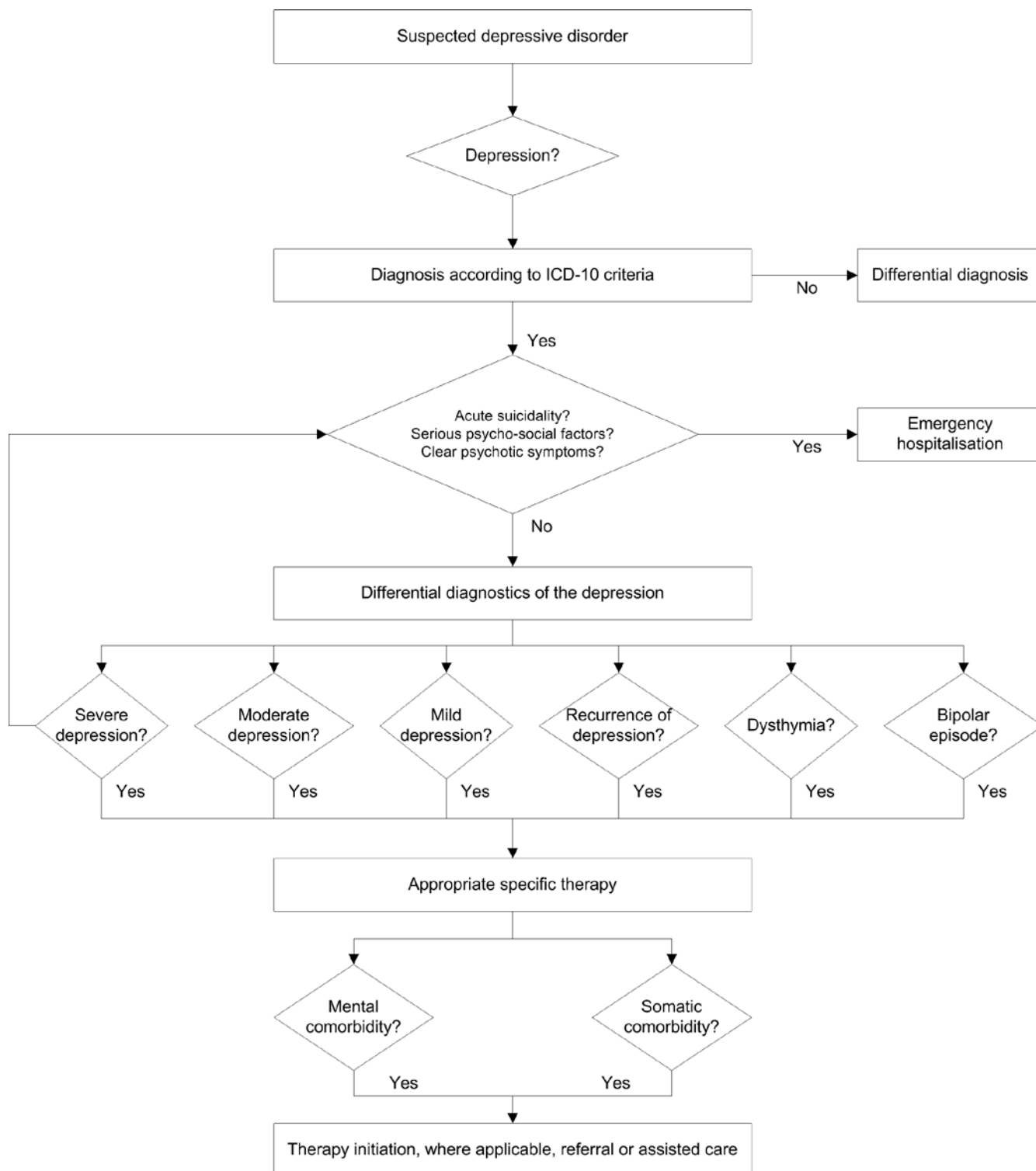
The scope of this guideline is **unipolar depressive disorders**, ie, **depressive episodes** (F32), **recurrent depressive disorders** (F33), **persistent affective disorders** (here only: **dysthymia**, F34.1) and **other affective disorders** (here only: **recurrent short depressive disorder**, F38.1) from the treatment age of 18 years up.

This guideline – like all other medical guidelines – is explicitly not a directive which is endorsed, written down and published by a legally authorized institution, and which regulates what must or must not be done in the legal territory under penalty of law.

A guideline is effective only, if the recommendations are applied to the individual patient. Prior to its use, the regional or local applicability of the guideline to the individual patient must be examined and, if necessary, the guideline be adapted.

The decision as to whether or not a particular recommendation will be followed, is to be made taking into account the individual situation of the patient and the available resources.

2 Diagnostics



Algorithm 1: Diagnostic process for depressive disorders

2.1 Diagnosis according to ICD-10

The ICD-10 defines **depressive disorders** under the diagnostic category “**mood [affective] disorders**” as psychopathological syndromes with specific duration.

Table 1: Main categories of mood [affective] disorders as per ICD-10

F30	Manic episode	F34	Persistent mood [affective] disorders
F31	Bipolar affective disorder	F38	Other mood [affective] disorders
F32	Depressive episode	F39	Unspecified mood [affective] disorders
F33	Recurrent depressive disorder		

The guideline refers to unipolar depressive disorder, i.e., depressive episode (F32), recurrent depressive disorder (F33), persistent mood [affective] disorders (here only: dysthymia, F34.1) and other **mood [affective] disorders** (here only: **recurrent short depressive disorder**, F38.1).

Recommendation/Statement	Grade of recommendation
2-1 To separate the different affective disorders and their severity both the current symptoms and the past course are decisive.	Statement

To diagnose a depressive disorder and determine its severity according to ICD-10 the following diagnostic criteria are relevant (see also Algorithm 2):

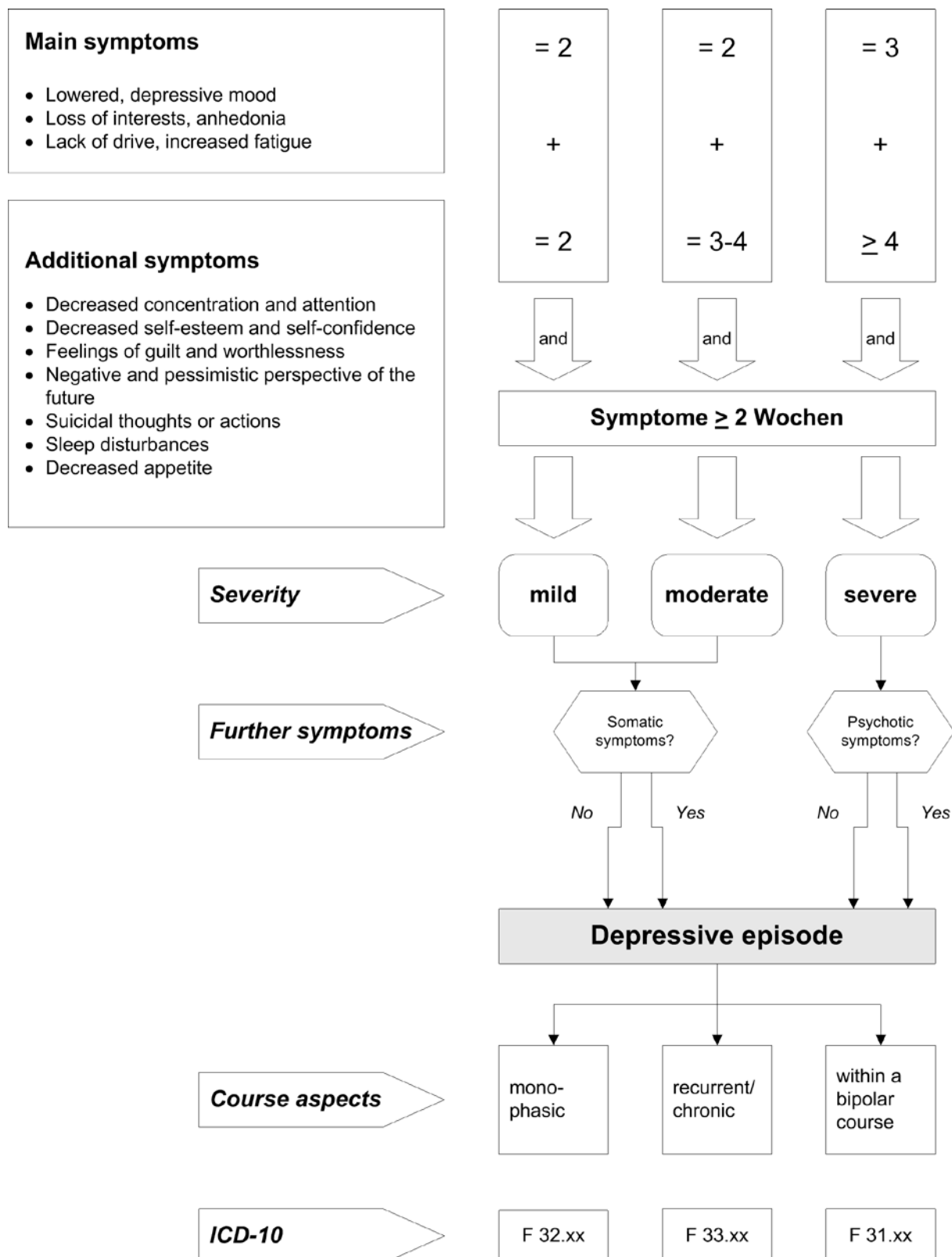
- **At least two (severe depression: three) main symptoms** must persist **at least 2 weeks**. Shorter periods may be respected, if the symptoms were abnormally severe or developed abnormally fast.
- Determination of severity: Patients suffer from at least two (mild episode, F32.0), three to four (moderate episode, F32.1) or at least four (severe episode, F32.2) other symptoms in addition to the main symptoms.
- The **somatic syndrome** in **mild** (F32.01) or **moderate depressive episodes** must be classified only, if **at least 4** of these symptoms are clearly detectable. In severe depressive episodes this additional coding is not indicated, because it is assumed that they include somatic symptoms, owing to their severity.
- A **severe depressive episode** can be further classified as “**with psychotic symptoms**” (F32.3), if delusional ideas (usually ideas of sin, pauperization, or a coming catastrophe), hallucinations, or depressive stupor occur.

A **recurrent depressive episode** of varying severity (F33.X) is characterized by a history of at least one other depressive episode in addition to the current one.

2.1.1 Subtyping: Somatic syndrome and psychotic symptoms

In mild or moderate depressive episodes the ICD-10 also allows classification based on presence of somatic syndrome in addition to the main and additional symptoms. Frequent characteristics of the **somatic syndrome** are:

1. Loss of enjoyment or interest in normally pleasant activities;
2. Lacking ability to be emotionally responsive to a friendly environment or joyful events;
3. Early morning awakening; two or more hours before the usual time;
4. Morning down;
5. The objective finding of a psychomotoric inhibition or agitation;
6. Clear loss of appetite;
7. Loss of weight, often more than 5% of the body weight in the previous month;
8. Clear loss of libido.



Algorithm 2: Diagnosis of depressive episodes according to the ICD-10 criteria

2.2 Detection of depressive disorders

Table 2: Complaints indicating a depressive disorder

- Generalized physical exhaustion, weariness;
- Trouble falling or staying asleep;
- Disturbed appetite, stomach ache, loss of weight, obstipation, diarrhoea;
- Diffuse headache;
- Feelings of pressure in throat and chest, globus sensation;
- Dysfunction of the heart, circulation (eg, tachycardia, arrhythmia, syncope), respiration (eg, dyspnoea), stomach and intestine;
- Dizziness, flickering in the visual field, impaired vision;
- Muscle tensions, diffuse neuralgiform pain;
- Loss of libido, suspension of menstruation, impotence, sexual dysfunctions
- Loss of memory

Recommendation/Statement	Grade of recommendation
<p>2-2</p> <p>The possibility of a depressive disorders, and/or, if applicable, of further symptoms of a depressive disorders should be actively explored, since rather than spontaneously reporting typical core symptoms of depression, patients tend to report unspecific complaints such as sleep disruptions with early awaking in the morning, poor appetite, general loss of energy, sustained pain and/or physical complaints.</p>	A

Table 3: Example questions to assess symptoms

Main symptoms	
Depressed mood	<p>"Have you been feeling down or sad in the past two weeks?"</p> <p>"Were there times when your mood was better or worse?"</p>
Loss of interests and apathy	<p>"Have you lost interest or enjoyment in important activities (job, hobby, family)?"</p> <p>"In the past two weeks, have you had the feeling of not longer being interested in anything?"</p>
Easy fatigability and loss of motivation	<p>"Have you lost your energy?"</p> <p>"Are you constantly feeling tired and down?"</p> <p>"Are you having trouble coping with everyday problems as usual?"</p>
Additional symptoms	
Reduced concentration and attention	<p>"Are you having difficulties concentrating?"</p> <p>"Are you having trouble reading the newspaper, watching TV or following a conversation?"</p>
Reduced self-esteem and self-confidence	<p>"Are you suffering from low self-confidence and/or low self-esteem?"</p> <p>"Are you feeling as self-confident as usual?"</p>
Feelings of guilt and worthlessness	<p>"Are you often self-reproachful?"</p> <p>"Do you often give yourself the blame for what happens?"</p>
Negative and pessimistic about future prospects	<p>"Does the future appear blacker than usual?"</p> <p>"Do you have plans for the future?"</p>

Suicidal ideation/ suicidal acts	<p>“Are you feeling so bad that you are thinking of death or have thoughts that you would be better off dead?”</p> <p>“Did you have or do you currently have concrete plans to harm yourself?”</p> <p>“Have you tried hurting yourself?”</p> <p>“Is there anything that keeps you alive?”</p>
Problems with sleep	<p>“Has your sleep changed?”</p> <p>“Are you sleeping more or less than before?”</p>
Reduced appetite	<p>“Are you having more/less appetite recently?”</p> <p>“Have you been losing weight unintentionally?”</p>

The presence of a depressive disorders is particularly likely in patients with one or more of the following risk factors.

Table 4: Risk factors for a depressive disorder

- Previous depressive episodes;
- A family history of bipolar or depressive disorders;
- A personal history or family history of suicide attempts;
- Comorbid somatic diseases;
- Comorbid substance abuse or comorbid substance dependence;
- Current stressful events in life;
- Lack of social support.

2.2.1 Screening for early detection

Recommendation/Statement	Grade of recommendation
<p>2-3</p> <p>In the care of patients belonging to a high-risk group – eg, patients with previous depressive disorders or comorbid somatic diseases – measures for the early detection of depression should be applied at contact with the family doctor and general hospitals.</p>	B
<p>2-4</p> <p>If a screening reveals increased depression scores, the diagnose of a clinically relevant depressive disorder should be established immediately by fully assessing the main and additional symptoms (severity), and by asking questions on the course and duration.</p>	B

Adequate instruments for the screening are the WHO-5-questionnaire about well-being, the Patient Health Questionnaire (PHQ-D), and the global depression scale ADS (Allgemeine Depressionsskala). Another option for quick evaluation of a possible depressive disorder is the so-called “two-questions-test”:

1. In the past month, have you often been feeling down, sad, depressed or hopeless?
2. Have you been experiencing much less interest or enjoyment in things that you otherwise enjoy?

If patient responds “yes” to either of these questions, the prime diagnostic criteria must be assessed, because only the **explicit recording of all relevant main and secondary symptoms allows the establishment of an adequate diagnosis according to ICD-10**. Generally, this involves a thorough verbal examination of the patient which may be based on the example questions in Table 5.

2.3 Differential diagnostics

The presence of depressiveness, exhaustion, sadness, self-doubt and resignation as well as the presentation of isolated symptoms of depression are not equivalent to a depressive disorder. **Depressive symptoms are typical for many mental disorders.**

In patients with **multiple mental and physical diseases** or **elderly patients** the diagnosis of a depressive disorder may be more difficult, because symptoms like general weakness or sleeping disturbances may occur independently of depression.

The following **screening questions**, which **refer to the past 4 weeks**, may be asked to differentiate against other suspected, non-depressive disorders or additional mental comorbidity, respectively.

Table 5: Examples of screening questions in the differential diagnosis

Panic disorder	"Did you ever have an anxiety attack when you felt overwhelmed by sudden intense anxiety, trepidation, or agitation?"
Generalized anxiety disorder	"Did you ever feel anxious, stressed and filled with fear and worry for at least a month or longer?"
Social phobia	"Did you ever have unfounded fears of talking to others, doing something in the presence of other people, or of being the centre of attention?"
Agoraphobia	"Did you ever suffer from causeless fears of using public transport, entering shops, or staying at public places?"
Post-traumatic stress disorder	"Did you ever experience any unusually terrifying or threatening incidence whose effects made you suffer for months?"
Specific phobia	"Did you ever go through a period when you were suffering from unfounded fears of specific situations, objects or animals?"
Obsessive-compulsive disorder	"Have you ever been bothered by thoughts that didn't make any sense, and kept coming back to you even when you did not want them to?"
Manic or hypomanic episodes	"Have you ever been unusually happy for several days, restless, or irritable so that your friends or relatives were worrying about you?"
Eating disorder	"Have you ever been extremely worried for months about how much you were eating, being too fat or losing weight?"
Alcohol abuse or dependence	"Did you ever go through a period when you were drinking five or more glasses of alcohol a day?"
Medication abuse or dependence	"Have you been taking repeatedly stimulants, tranquillizers, sleeping pills or pain killers without medical prescription or in higher dosages?"
Drug abuse or dependence	"Have you ever repeatedly taken drugs in your life, eg, cannabis, ecstasy, cocaine or heroine?"

2.3.1 Suicidality

8.6% of all patients hospitalized due to suicidality and 4% of all patients hospitalized due to a depressive disorder (without specific suicidality) die through suicide. 60-70% of patients have suicidal thoughts during a depressive episode. The **active and empathic evaluation of suicidality** is therefore particularly important **in the course of the first diagnostic attempt**. In the course of further treatment, when suicidality may newly develop, **regular assessments** are also necessary.

The evaluation of suicide risk should be performed by asking about risk markers:

- „Have you been thinking recently that you don't want to live anymore?"
- „Often?"

- „Did you think about it unintentionally? That is to say: Have you been bothered by suicidal thoughts?“
- “Have you been able to push these thoughts aside?“
- “Do you have concrete ideas how you would do it?“
- “Did you make any preparations?“
- “To put it another way, is there anything that keeps you from doing it?“
- “Did you talk to anyone about your suicidal ideas already?“
- “Did you ever try to kill yourself?“
- “Has anyone in your family or any friends or acquaintances committed suicide?“

Recommendation/Statement	Grade of recommendation
2-5 In any patient with a depressive disorder, suicidality should be assessed routinely at every patient contact and, if applicable, be explored.	CCP
2-6 Patients with acute suicide risk and with reduced competence to adhere to agreements should be referred for psychiatric therapy, providing the individually required safety precautions.	A

2.3.2 Diagnostic approach in the presence of comorbidities

2.3.2.1 Mental comorbidities

Recommendation/Statement	Grade of recommendation
2-7 Depressive disorders often occur simultaneously with other mental disorders	Statement

Depressive disorders are frequently associated with **anxiety and panic disorders, somatoform disorders, substance abuse, eating and personality disorders**. Any **additional psychological diagnostic investigations are not indicated *per se***. Whether diagnosis of another disorder is indicated is dependent upon concrete suspicion. If a suspicion is confirmed through screening questions (**see examples of screening questions for differential diagnosis**), the active exploration of symptoms must continue.

2.3.2.2 Somatic comorbidities

Many **somatic diseases** (e.g., malignancies; musculoskeletal, endocrine, cardiovascular and pulmonary diseases, metabolic disorders, allergies, infectious diseases, cerebral diseases) may be associated with depressive symptoms.

Recommendation/Statement	Grade of recommendation
2-8 Depressive disorders require the thorough evaluation of somatic diseases, drug consumption, noxae associated with depressive symptoms, as well as comorbidities. In patients continued solely on psychotherapy, the physical status should be reliably investigated.	B
2-9 After eliciting the current depressive symptoms, a comprehensive anamnesis and diagnosis of further mental and/or somatic diseases should occur.	B
2-10 If a somatic comorbidity is likely to complicate the disease, the patient should be referred to a specialist, and in complications arising mental comorbidity, to a specialist or psychotherapist.	0

2.4 Stepwise diagnostic approach

Major symptoms (disorder of mood, drive, and/or activity) present?

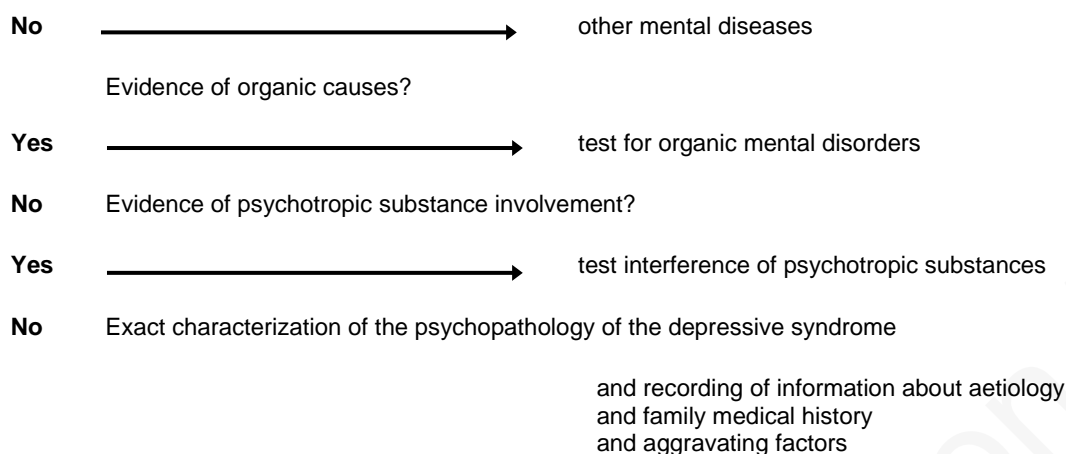


Figure 1: Diagnostic procedure for unipolar depressive disorder

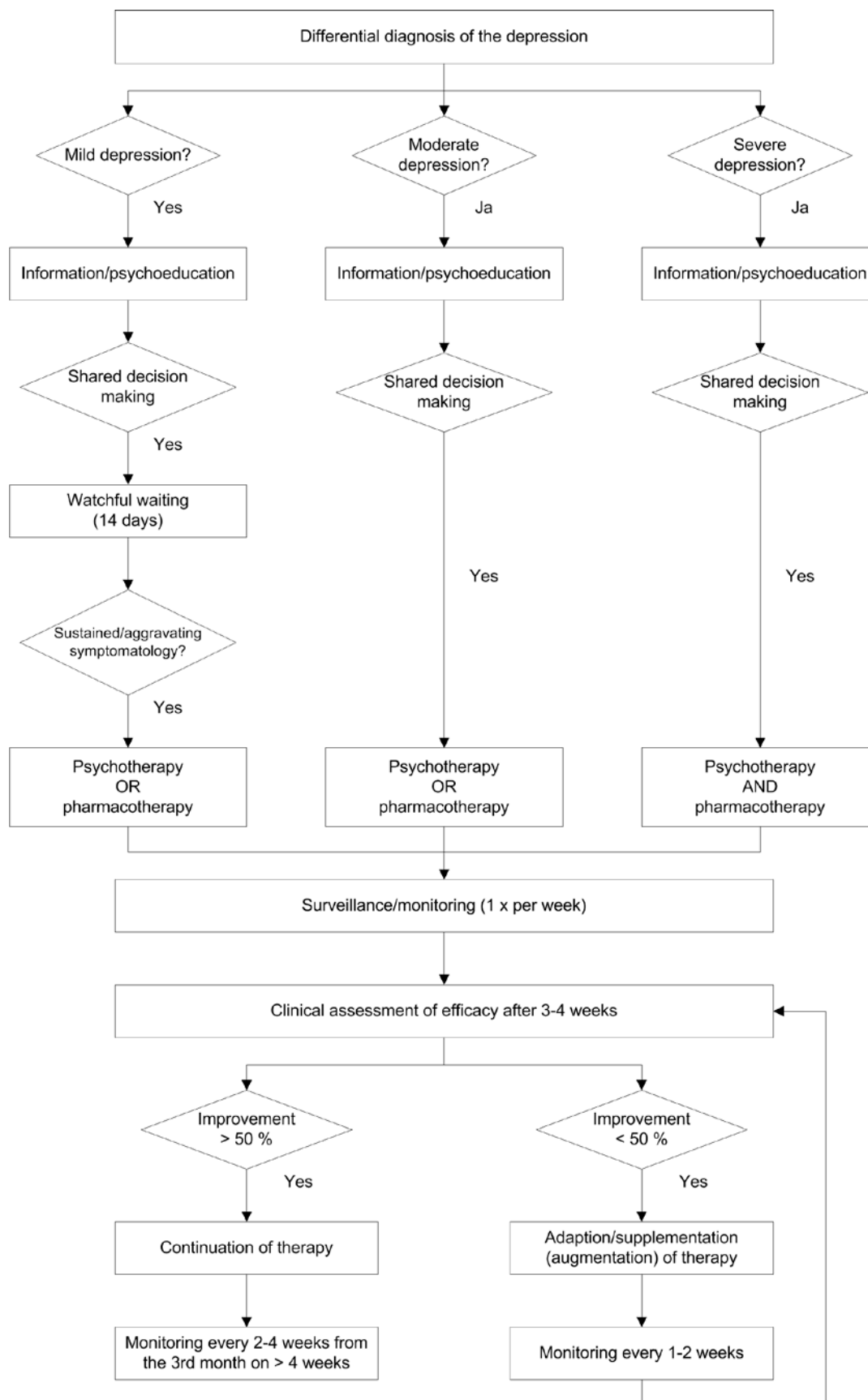
2.5 Ongoing Diagnostics

The therapy of unipolar depression requires **continuous diagnostic investigations throughout the treatment and process evaluation**. Especially during acute treatment a **regular monitoring of the therapy is necessary**.

Appropriate self-assessment tools are the Patient Health Questionnaire (PHQ-D), the Beck Depression Inventory (BDI), the Hospital Anxiety and Depression Scale (HADS), the Diagnostics of Depression Questionnaire (Fragebogen zur Depressionsdiagnostik [FDD]), the global depression scale ADS (Allgemeine Depressionsskala), and the Geriatric Depression Scale (GDS) in elderly patients. The Hamilton Depression Rating Scale (HDRS), the Bech-Rafaelsen Melancholia Scale (BRMS) and the Montgomery-Asberg Depression Rating Scale (MADRS) are clinician-administered assessment tools.

Recommendation/Statement	Grade of recommendation
2-11 If there is no positive response to therapy with respect to the treatment objectives within 3-4 weeks, an ineffective treatment should not be continued unaltered.	0

3 Therapy



Algorithm 3: Therapy of depressive disorders

3.1 Treatment goals and treatment strategies

The **general treatment** goals for patients with depressive disorders are:

- to reduce the symptoms of the depressive disorder and ultimately to achieve a complete remission;
- to reduce mortality, in particular due to suicide;
- to restore professional and psychosocial productivity;
- to re-establish the mental balance and
- to reduce the probability of a immediate relapse or later recurrence.

The **choice of the appropriate treatment alternative** depends on *clinical factors, such as symptom severity, course of the disease and the patient's preference*.

Generally there are four primary treatment strategies:

- **watchful waiting;**
- **drug intervention;**
- **psychotherapy;**
- **combination therapy.**

Other therapies are *electroconvulsive therapy, light therapy or sleep restriction therapy, sport- and movement therapy or occupational therapy*. In addition, procedures such as art therapies are applied.

3.1.1 Treatment phases and phase-specific treatment goals

The treatment of a mild depressive episode may be deferred, if patients decline treatment or the depressive symptoms are expected to resolve without therapy (**"watchful waiting"**). Still, the symptoms should be re-evaluated **within the next two weeks**.

The treatment of a depression, especially of a recurrent depression, may be separated into three phases: **acute therapy, maintenance therapy** (in case of sole pharmacotherapy: four to nine months after remission; in case of sole psychotherapy: eight to twelve months after remission) and **long-term/recurrence prophylaxis**.

Prophylaxis in recurrent depression is not necessary for all but only for patients with

- increased risk of a depression recurrence and/or
- biographically acquired unfavourable factors that are driving the disorder and reduced capacities to cope, which may both trigger further crisis and chronification.

Table 6: Definition of symptom changes

Response	Reduction of the depressive symptoms by 50% on standard scales from treatment initiation
Remission	Complete restoration of the original functional state or largely symptom-free after acute therapy
Relapse	Re-appearance of a depressive episode during the maintenance therapy
Complete recovery	Symptom-free for about 6 months after remission
Recurrence	Re-appearance of a depressive episode after complete recovery

3.1.2 Involvement of patients and relatives

Recommendation/Statement	Grade of recommendation
3-1 When talking to patients and relatives, the language should be understandable. Where medical terminology is used, it should be explained.	A

3-2 Patients and relatives should be advised of self-help and relative support groups and, where appropriate, be encouraged to participate.	A
3-3 Depressive patients should be advised of the symptoms, course, and treatment of the depression. This may also be appropriate for the relatives, if the patient agrees.	A

3.1.2.1 Shared decision making

Recommendation/Statement	Grade of recommendation
3-4 Beyond the legal obligation to inform the patient, potential treatment strategies and the desired effects and potential risks involved should be discussed with the patient, in line with shared decision making.	B

Table 7: Steps in shared decision making

Step 1	Inform about the diagnosis, course, and prognosis of the disease; offer shared decision making
Step 2	Point out the equivalence of potential treatment options ("Equipoise")
Step 3	Describe the treatment options and risks
Step 4	Explore the understanding, thoughts, and fears of the patient
Step 5	Understand the expectations and various preferences in the decision-making process
Step 6	Discuss, make or defer a decision
Step 7	Agree on the follow-up

3.1.2.2 Psychoeducation

Recommendation/Statement	Grade of recommendation
3-5 Psychoeducation should be offered as sensible addition to patients and their relatives to improve knowledge, acceptance, and patient cooperation within the overall treatment strategy.	B

3.2 Coordination of care and interaction between the care providers

3.2.1 Care providers

The **central care providers** for depressive diseases are:

- Family practitioners (general practitioners or specialists in internal medicine);
- Specialists for psychiatry and psychotherapy or neurology, respectively;
- Specialists for psychosomatic medicine and psychotherapy;
- Physicians with additional qualifications in psychotherapy and psychoanalysis;
- Psychological psychotherapists;
- Other providers of psychosocial therapies (occupational therapists, social workers and – pedagogues, sociotherapists, psychiatric home care);
- Specialist hospitals and departments in general hospitals for psychiatry and psychotherapy or psychosomatic medicine and psychotherapy in general hospitals, including affiliated institutions and university outpatient clinics and specific centres, eg, gerontopsychiatric;
- Rehabilitation centres (especially psychosomatic rehabilitation clinics).

In addition, self-help groups of patients and their relatives have been formed in many places.

3.2.2 Treatment interfaces

The following indication criteria for different levels of care are useful:

After state-of-the-art somatic, psychopathological and psychological diagnostics, **mild and moderate depressive disorders** may be treated as entirely outpatient by all relevant treatment groups, ie, family doctors or specialists for psychiatry and psychotherapy as well as psychosomatic medicine and psychotherapy, or neurologists, physicians with additional qualifications in psychotherapy and psychoanalysis or psychological psychotherapists.

If the treatment by a family doctor does not lead to sufficient improvement within at most 6 weeks after treatment initiation, the consultation of a specialist or medical or psychological psychotherapist must be considered. If **psychotherapeutic treatment is not successful**, the consultation of a specialist is recommended, at latest after three months.

In addition to the difficulties described above, the referral or joint treatment to/by a specialist for psychiatry and psychotherapy or neurologist is recommended in case of

- Unclear psychiatric differential diagnostics;
- Severe symptoms;
- Therapy resistance;
- Problems during pharmacotherapy and/or psychotherapy;
- Drug interaction problems during combined use of antidepressants and other drugs;
- Acute risk to self and others;
- Psychotic symptoms or depressive stupor;
- Comorbidity of a depressive disorder with another severe mental disorder or severe somatic disease.

If treatment by a multi-speciality team is necessary, the referral to a psychiatric outpatient institution providing complex treatment programs should be evaluated.

Psychological psychotherapists and specialists for psychosomatic medicine and psychotherapy generally provide guideline-oriented psychotherapy. Referral to the personnel mentioned above is also recommended

- to receive psychotherapy as part of a combination therapy if the symptoms are severe
- in patients resistant to therapy but open to psychotherapy
- in comorbidities of depressive disorder and another severe mental disorder;
- for psychotherapeutic (co-)treatment;
- in case of problems during psychotherapy;
- during psychotherapy, in the comorbidity of depression and chronic somatic disease.

Specialists for psychosomatic medicine and psychotherapy as well as medical psychotherapists may also be consulted regarding pharmacotherapy unless they offer psychotherapy only, and if suitably qualified, especially if a combination of pharmacotherapy and psychotherapy is used already.

In severe and/or chronicized depression psychotherapy (by a specialist or psychological or medical psychotherapist) is usually indicated in addition to professional pharmacotherapy.

The acute risk of suicide or danger of hurting others, together with clear psychotic symptoms and a lacking or limited ability to keep with agreements constitute **emergency commitment for inpatient psychiatric-psychotherapeutic treatment**.

Psychiatric-psychotherapeutic inpatient care is indicated

- if the depression involves the danger of isolation and other serious psychosocial factors;
- if personal circumstances strongly interfere with treatment success;
- in therapy resistance to outpatient care;
- if there is a strong risk of (further) chronification;
- if the clinical picture is so severe that outpatient care is not sufficient.

If in such a case psychotherapy is preferentially offered, **psychiatric-psychotherapeutic inpatient care may also be indicated**.

As per social code SGB IX, **inpatient rehabilitation treatment is especially indicated**, if the therapy aims to stabilize treatment outcomes, to treat disease effects, to improve coping with the (chronic or chronicized) disease, or to improve or regain work productivity.

Outpatient occupational therapy under the terms of the guideline policy for therapeutic products is particularly indicated, if measures are necessary to improve or maintain autonomous life and/or basic work productivity.

Sociotherapy or psychiatric home care are indicated in particular if the symptoms are severe and involve considerable disruption of function and participation.

Criteria that facilitate or disclose the decision on the **referral to consultation services or follow-up treatment** are important in this context. Within the **acute and maintenance therapy** questions arise on the cooperation of family doctors, specialists, medical and psychological psychotherapists as well as specialty clinics. Other care providers that need to cooperate are outpatient institutions and day clinics, outpatient institutes, inpatient and outpatient rehabilitation centres as well as providers of psychosocial therapies, eg, practice-based occupational therapists or outpatient cares including sociotherapy or psychiatric **home care**.

The *Algorithm for the Diagnostic Process* of depressive disorders illustrates the diagnostic process with the respective interfaces and levels of cooperation. To distinguish the various depressive disorders and their severity both the current clinical picture and course of disease are important. This enables a diagnosis relevant to the treatment of the depressive disease by **directly and completely assessing the main and additional symptoms** and by **asking questions on the course, severity and presence of somatic or psychotic symptoms**. The differential-diagnostic separation is especially important for **bipolar disorder, psychotic disease, addictive disorder, and dementing illness**. Since many other diseases are also associated with depressive symptoms, a comprehensive anamnesis of further mental disorders and somatic diseases is necessary after the current depressive symptoms have been defined.

The core treatment goals are **complete symptom remission and relapse prophylaxis**. The patient has to be included in the decision about the optimal treatment plan, according to the concept of **shared decision making**. Following the acute therapy, treatment should be continued for four to nine months to maintain the treatment effects and reduce the risk of a relapse (maintenance therapy) – see also *Algorithm Therapy of Depressive Disorders*. In the case of **first clinical manifestations**, the intensity of the therapy may be reduced carefully after the maintenance therapy. Long-term relapse prophylaxis is indicated in **recurrent depression**, either as singular pharmaco- or psychotherapy or as combination therapy of drug intervention and psychotherapy.

In psychotherapy, eg, guideline-policy compliant psychotherapy, there is no such separation into acute treatment, maintenance treatment and long-term relapse prophylaxis, because symptom alleviation and prophylactic therapeutic elements are more closely connected. Besides pharmacotherapy and psychotherapy, other treatment methods are available.

3.3 Pharmacotherapy

3.3.1 Substance groups and effectiveness

Many drugs are approved in Germany for the acute treatment of depressive disorders, classified according to their specific mechanism of action.

The most important **substance groups** are (see also Appendix 3: “Antidepressants – drugs classified by substance group and their dosage, plasma level and monitoring”):

- Tri- (and tetra-) cyclic antidepressants (TCA) or nonselective monoamine-reuptake inhibitors (NSMRI);
- Selective serotonin-reuptake inhibitors (SSRI);

- Monoamine oxidase (MAO) inhibitors;
- Selective serotonin-/noradrenalin-reuptake inhibitors (SSNRI);
- Selective noradrenalin-reuptake inhibitors (SNRI);
- Alpha2-receptor antagonists;
- Selective noradrenalin-dopamine-reuptake inhibitors (Bupropione);
- Melatonin-receptor agonist (MT1/MT) and serotonin 5-HT_{2C}-receptor antagonist (Agomelatine).

Furthermore there are unclassified antidepressants (Trazodon), lithium salts and phytopharmaceuticals (St.John's Wort).

Further substances, eg, benzodiazepine and antipsychotics, are atypical antidepressants but are important in practice and are used in the treatment or in specific situations.

Efficacy in mild depression: Because there are no statistically significant differences between placebo and antidepressant, only few patients are expected to benefit from the treatment with antidepressants.

Efficacy in moderate to severe depression: the difference between placebo and antidepressant is greater. In the most severe cases up to 30% of the treated patients benefit from antidepressants, ie, beyond the rate determined for placebo.

There are **major differences** in **toxicity** and **side effects** between the substance classes. The latter is of profound clinical relevance, as more than half of the patients treated with antidepressants suffer from undesired side effects.

Onset of effect and process of improvement: Antidepressants do **not** act faster than placebo. However, antidepressants trigger the healing process in significantly more patients than placebo (10-30% more in moderate to severe depression). If adequately dosed, the **onset of effect of antidepressants is fast**, eg, **within the first two weeks** of treatment in 70 % of all responders. If no improvement is observed during the first two weeks of treatment, the probability of a clinical response declines to <15 %. After three weeks without improvement the probability is already <10 %. At this point at the latest, the treatment should be modified, either by increasing the dose, adding another drug, or switching the drug.

3.3.2 Principles in acute treatment

Pharmacotherapy generally holds the best prognosis, if a trusting relationship has been established between patient and therapist or is being pursued as important treatment stage. Confidence in the therapist is also important in attaining patient cooperation; this is especially relevant in the successful monitoring and prevention of drug side effects. From the beginning on, pharmacotherapy is embedded in the appropriate discussions.

3.3.2.1 Mild depressive episodes

Recommendation/Statement	Grade of recommendation
3-6 In a mild depressive episode depression-specific treatment may be deferred ("watchful waiting"), if the symptoms can be assumed to resolve without active treatment. If the symptoms continue or worsen after 14 days, the decision for a specific therapy should be made with the patient.	0
3-7 Antidepressants should not be used generally in the initial treatment of mild depressive episodes, but only after carefully weighing the benefit-risk ratio.	B
3-8 The use of antidepressants in mild depressive episodes may be justified by: <ul style="list-style-type: none"> • Wishes/preferences of the patient • Positive experiences of the patient through good response to a previous drug therapy • Persistence of symptoms after other interventions • Depressive episodes of moderate or severe intensity in the patient history. 	Statement

3.3.2.2 Moderate and severe depressive episodes

Antidepressants are indicated especially in the treatment of *moderate and severe depressive episodes*. In this regard, all approved chemical antidepressants show similar efficacy in outpatient use, but differ in the side-effects and interaction profile.

Recommendation/Statement	Grade of recommendation
3-9 For the treatment of acute moderate depressive episodes, patients should be offered antidepressant drug therapy.	A
3-10 In acute severe depressive episodes, combination treatment with pharmacotherapy and psychotherapy should be offered.	A
3-11 If pharmacotherapy is considered in mild or moderate depressive episodes, an initial therapy with St.John's Wort may be attempted as well, keeping in mind the specific side effects and interactions.	O
3-12 Patients taking St.John's Wort should be informed about the different strength of the available formulations and the resulting uncertainties. In addition they should be advised of the potential for severe interactions between St.John's Wort and other drugs (including contraceptives, anticoagulants and anti-epileptic drugs).	B

3.3.2.3 Selection of antidepressants

Table 8: Criteria for the selection of antidepressants

Tolerability	<ul style="list-style-type: none"> • Different side-effect profiles of SSRI and TCA, especially in outpatient care, compared with conventional, older TCA; • tolerability of TCA and SSRI barely different in inpatient care; • qualitatively different side-effect profile of TCA and SSRI (serious complications more frequent under TCA, eg, delirium, cardiac block/arrhythmia, retention of urine); • when prescribing antidepressants to female patients the lower tolerability of imipramin must be taken into account.
Overdose risk	<ul style="list-style-type: none"> • The intake of a one week's supply of TCA may be lethal in suicidal patients; in outpatient care, thus, prescription of small packaging sizes only.
Response in previous use	<ul style="list-style-type: none"> • Efficacy and tolerability of previous treatments with antidepressants should be taken into account in new occurrences.
Drug regimen	<ul style="list-style-type: none"> • When compared with SSRI or newer antidepressants, TCA require more individualized titration and control (step-wise up-titration, plasma level, ECG control); • Step-wise up-titration also makes sense for SSRI and newer antidepressants such as venlafaxin and mirtazapin.
Practical drug experience	<ul style="list-style-type: none"> • The physician's experience with specific antidepressants is relevant to the selection of the drug.
Options if treatment fails	<ul style="list-style-type: none"> • For TCA the measurement of serum levels is useful, because the therapeutic serum levels are known for most TCA. The administration of high doses may be useful for TCA, because there is a dose-effect relationship.
Comorbidity and comedication	<ul style="list-style-type: none"> • Comorbidity: see information on elderly patients under "pharmacotherapy in special patient groups", comedication see "drug interactions in the long version"; • if there is comorbidity with obsessive-compulsive disorder: SSRI or Clomipramin

	<ul style="list-style-type: none"> • If there is comorbidity with ADHS: NRI.
Patient' preferences	<ul style="list-style-type: none"> • Because patients may respond differently to antidepressants regarding benefits and side effects, physically and psychologically, the subjective significance of the undesired side effect is important when choosing the drug.

3.3.2.4 Initiation of therapy

Recommendation/Statement	Grade of recommendation
3-13 When starting treatment, antidepressants always should be dosed low ("initiation dose"). In elderly patients, it is useful to halve the initiation dose and, if necessary, uptitrate the dose slowly.	Statement
3-14 If tricyclic antidepressants are used, the anticholinergic and chinidine-like side effects must be kept in mind. Thus, their administration is more risky in patients with cardiovascular disease, narrow angle glaucoma, prostatic hypertrophy, pyloric stenosis and other pronounced intestinal stenosis, severe obstipation, cognitive disorders, convulsive disorders or states of confusion/delirium.	Statement
3-15 Especially at the start of therapy with SSRI particular attention should be paid to <ul style="list-style-type: none"> • clues to a serotonin syndrome (confusion, delir, shaking/shivering, sweating, change of blood pressure, myoclonus and mydriasis); • bleeding tendency associated with administration of nonsteroidal antirheumatics; • hyponatremia, especially in elderly patients (SIADH=increased production or effect of the antidiuretic hormone ADH); • diarrhoea; • suicidal ideation; • considerably increased motor agitation, anxiety and agitation. Patients should be advised at the beginning of the therapy that these symptoms may occur and if so, to consult a doctor.	B
3-16 Intensive instruction and frequent monitoring (weekly) is recommended during the first four weeks in order to encourage the patient to participate.	CCP
3-17 The conversation with the patient should <ul style="list-style-type: none"> • identify and allay concerns regarding antidepressants (eg, development of addiction or tolerance, personality changes); • explain the biological mechanisms of action; • advise on effect latency and potential interactions with other drugs; • explain side effects; • justify the duration of treatment; Here it can be advantageous to involve relatives and/or self-help groups.	Statement

3.3.2.5 Efficacy assessment and therapy monitoring

Recommendation/Statement	Grade of recommendation
<p>3-18</p> <p>Monitoring is recommended weekly during the first four weeks of treatment, afterwards every 2-4 weeks and after three months at longer intervals.</p> <ul style="list-style-type: none"> • After a maximum of 3-4 weeks, the efficacy should be thoroughly evaluated and it should be decided whether a change or supplementation of the treatment strategy is indicated or not. • If no improvement is apparent, patient cooperation and plasma levels (if appropriate) should be checked. • Generally the testing of plasma levels is indicated if the maximum dose is used, tolerability problems occur, patients are on various drugs or comorbid, the symptoms worsen under stable dose of antidepressant, and in nonresponders or in the case of insufficient cooperation. • The monitoring of serum concentrations of antidepressants is only well established in tricyclic and tetracyclic substances. • At the start of antidepressant treatment, blood counts and transaminases should be measured. • Initially and in the course of treatment with lithium creatinine, creatinine clearance, electrolytes, thyroid size as well as TSH values are important. • The monitoring of body weight is important for some drugs due to the risk of weight increase, especially under mirtazapin and most of the tricyclics (eg, trimipramin and amitriptylin) as well as lithium. • Because of the chinidine-like effects of TCA on conduction, and the risk involved of cardiac block and arrhythmia, ECG monitoring is necessary before treatment initiation, after up-titration and, dependent on dose and individual risk, also during treatment. • In the beginning of treatment, attention should be paid to every patient treated with antidepressants for possible symptoms indicating elevated risk of suicidality. • The discontinuation of antidepressants should be performed by step-wise reduction over a period of four weeks. 	<p>Statement</p>

3.3.2.6 Drug discontinuation

Antidepressants should be reduced **step-wise over a period of four weeks**. Sometimes more time is needed. Fluoxetine, however, can be discontinued more quickly due to its very long half-life.

As long as the side effects resulting from discontinuation are mild, patients should be reassured and the symptoms monitored.

If symptoms are severe, the reinstatement of the effective dose of the original antidepressant should be considered (or another one with longer half-life from the same substance class) and then be discontinued even slower under supervision.

3.3.2.7 Maintenance therapy

Recommendation/Statement	Grade of recommendation
<p>3-19</p> <p>Antidepressants should be continued at least 4-9 months beyond the remission of a depressive episode, because this substantially reduces the risk of a relapse. In the maintenance phase the same dose should be used as in the acute phase.</p>	<p>A</p>

Dose **reduction implies an increased risk of relapse**. To finish the remission-stabilizing treatment it has proved useful to taper down the antidepressant to avoid discontinuation symptoms.

3.3.3 Recurrence prophylaxis

Recommendation/Statement	Grade of recommendation
3-20 Patients with a recent history of two or more depressive episodes including considerable functional limitations should be instructed to take the antidepressant for at least 2 years for long-term prophylaxis.	B
3-21 For recurrence prophylaxis the same dose of antidepressant should be administered as in the acute therapy.	O
3-22 In suicidal patients, recurrence prophylaxis with lithium should be considered to reduce suicidality (suicide attempts and suicide).	A

3.3.4 Measures in nonresponsive patients

3.3.4.1 Determination of serum levels and therapeutic drug monitoring

Differences in metabolism/enzyme activity may mean that therapeutic drug serum concentrations (plasma level) are not reached, even though the drug was administered as specified.

Recommendation/Statement	Grade of recommendation
3-23 If a patient does not respond to antidepressant monotherapy after 3-4 weeks, the reasons for this should be evaluated. Potential reasons include insufficient cooperation of the patient, inappropriate dosing, or low serum levels.	O

3.3.4.2 Increasing the dose

Recommendation/Statement	Grade of recommendation
3-24 For many antidepressants (eg, TCA, venlafaxin, tranylcypromin) nonresponse may be approached by uptitrating the substance according to the drug label instructions. This does not apply to SSRI.	O

If increased dose does not suffice, one of the following strategies can be considered:

- Increase the antidepressant's effect by adding another substance that is not an antidepressant. This measure is called "**augmentation**".
- Switch to another antidepressant. This measure is called change or "**switching**".
- The addition of another antidepressant to existing insufficient treatment. This measure is called "**combination**".
- **Combination with psychotherapy** or, if appropriate, **change to psychotherapy**.

3.3.4.3 Augmentation

Recommendation/Statement	Grade of recommendation
3-25 In patients not responding to an antidepressant, augmentation with lithium may be attempted by an experienced physician.	B
3-26 If a patient does not respond to lithium 2-4 weeks after reaching therapeutic lithium levels, lithium should be discontinued.	CCP
3-27 Patients showing good response to an antidepressant augmented with lithium should continue this regimen for at least 6 months.	B

3-28 The augmentation of an antidepressant with carbamazepine, lamotrigine, pindolol, valproate, dopamine agonists, psychostimulants, thyroid- or other hormones is not recommended on a routine basis in therapy resistant depression.	0
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3.3.4.4 Switching the antidepressant

When changing to an antidepressant of another substance class, initially a single substance should be prescribed. Switching the antidepressant is the most common strategy in the therapy of nonresponders. However, the efficacy of this method is only poorly supported by studies. It is **preferentially recommended to switch the substance class when changing the antidepressant**.

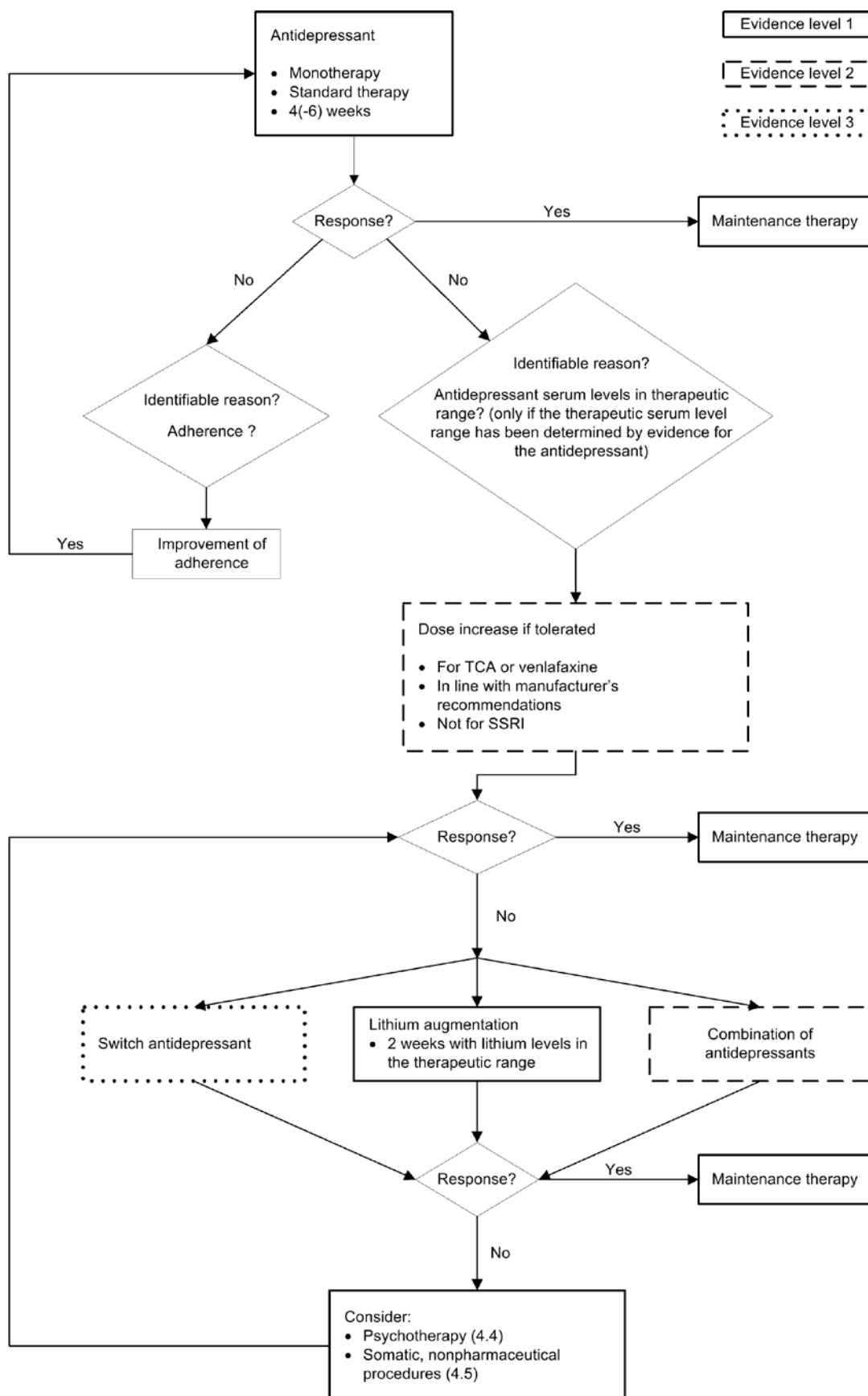
Recommendation/Statement	Grade of recommendation
3-29 When switching between antidepressants, the new drug should be step-wise uptitrated and the prior drug tapered down to avoid potential interactions.	B
3-30 Because switching antidepressants is not the method of choice in nonresponse, each switch should be carefully evaluated.	B
3-31 If changing from SSRI, SNRI and clomipramine to MAO-inhibitors a safe margin of 2 weeks should be allowed, or 5 weeks, respectively, for fluoxetine. A combination of MAO-inhibitors with these antidepressants is contraindicated.	Statement

3.3.4.5 Combining antidepressants

The combination of one antidepressant with another may be useful in patients whose depression turned out to be therapy-resistant and who are willing to accept possible side effects.

There is no evidence of therapeutic value from the prescription of more than two different antidepressants.

Recommendation/Statement	Grade of recommendation
3-32 In patients nonresponsive to antidepressant monotherapy, only the combination of mianserine (considering the risk of agranulocytosis) or mirtazapine with an SSRI or alternatively a TCA can be recommended. Only this combination has been shown to be more effective than the respective monotherapies in several randomized and double-blind studies.	Statement



Algorithm 4: Drug therapy of treatment-resistant depression

3.3.5 Pharmacotherapy of chronic depression

Recommendation/Statement	Grade of recommendation
3-33 In dysthymia and double depression, it should be checked whether pharmacologic treatment is indicated.	A
3-34 In chronic (persisting more than 2 years) depressive episodes, pharmacological treatment should be considered.	B

3.3.6 Use of other substances

Antipsychotics are only indicated in *psychotic depression*, because of the side-effects (risk of tardive dyskinesia, increase of weight, diabetes mellitus, etc.) and insufficient evidence of efficacy. This also applies to conventional depot antipsychotics (eg, *fluspirilene*, *haloperidol-decanoate*), which are associated with an increased risk of tardive dyskinesias.

Benzodiazepines have practically **no antidepressant effect**, and they are not approved for the treatment of depression. In the end, the indication for benzodiazepine therapy must be considered on a case-by-case basis and possible risks be discussed. The use of benzodiazepines should be short-term only (below 4 weeks).

3.3.7 Pharmacotherapy in special patient groups

3.3.7.1 Elderly patients

Recommendation/Statement	Grade of recommendation
3-35 There is evidence that antidepressants are also effective in elderly patients. The elderly should be therefore treated as for younger patients. The side-effect/tolerability profile in elderly is even more important compared to younger patients. Differences in efficacy between the two large groups of antidepressants, TCA and SSRI, and also among other, newer antidepressants (eg, moclobemide, venlafaxine, mirtazapine) have not been documented. In elderly patients low doses should be used to initiate treatment with TCA.	Statement

In elderly patients receiving lithium salts **neurotoxic reactions** are more frequent and have been especially reported in combination with other psychopharmaceuticals (classic and atypical antipsychotics).

3.3.7.2 Dementia

Recommendation/Statement	Grade of recommendation
3-36 Generally, patients with depression and concurrent organic brain diseases may be treated with antidepressants in the same way as elderly patients without organic brain disease. However, drugs with sedating and/or anticholinergic effects should be avoided.	0

Very little data are available supporting the superiority of antidepressants versus placebo in the treatment of depression in patients with dementia. If necessary, substances lacking anticholinergic mechanisms should be used. It appears to be justified to treat patients with severe depression or a history of depression in the same way as other elderly adults. Where possible, the same drug that proved to be effective in previous treatments should be used.

3.3.7.3 Pregnancy and breast feeding

If a patient with **existing recurrent depression plans to get pregnant**, the **risks and benefits need to be balanced carefully**. If the individual risk of recurrence is high, a low-dose monotherapy is also advisable during pregnancy, after considering the consequences of a recurrence.

The choice of drug before or during pregnancy, or during breast feeding depends largely upon the hazards to the baby generated by drug teratogenicity or distribution of the substance into breast milk. *Lithium* may cause *cardiac malformations*, ie, *Ebstein's anomaly*, in the embryo. Also the antiepileptics *valproic acid* and *carbamazepine* are teratogenic, eg, causing *malformations of the heart and skeleton*.

Women on antidepressive drugs should preferentially give birth in a maternity clinic with a neonatology facility, to assure intensive monitoring of the baby at any time in the case of withdrawal and side effects.

If the risks and benefits are carefully considered, breast feeding is generally compatible with antidepressant therapy.

Finally, the addition of psychotherapy or a complete switch to **psychotherapy** may be considered as an alternative for treatment-naïve patients or patients who have been treated with pharmacotherapy.

3.3.7.4 Depression in perimenopause

In **middle-aged women** affective disorders are often attributed to hormonal changes during perimenopause. Currently, **no recommendations can be given on the use of hormone therapies or so called hormone replacement therapies** in the treatment of depression.

3.3.7.5 Psychotic depression

Severe depressive disorders may be associated with psychotic symptoms, eg, delusional ideas and/or hallucinations. In psychotic depression often a combination of antidepressants and antipsychotics is used. This recommendation is based on general clinical practice rather than stringent clinical studies. Patients with psychotic depression require co-monitoring by a qualified psychiatrist.

Recommendation/Statement	Grade of recommendation
3-37 In patients with psychotic depression, the co-administration of an antidepressant with an antipsychotic should be considered. However, the optimal dose and duration of treatment is not known for these drugs.	B

3.4 Psychotherapy

Psychotherapy is the treatment of individuals, predominantly based on psychological methods. Using different procedures, psychotherapy has been widely established in the treatment of depressive disorders, in outpatient, day-hospital and inpatient care. Possible **undesired and hazardous effects** need to be considered in psychotherapy, eg, stating the wrong diagnosis, failure due to unprofessional practices, or insufficient "compatibility" between the patient's- and therapist's personality as well as unethical behaviour of the therapist.

Basic psychotherapeutic treatment of depressive disorders involves the following aspects:

- Active, flexible and supportive approach; encouraging and conveying hope;
- Empathic establishment of contact, building a trusting relationship;
- Exploration of the subjective disease model, clarification of current motivation and therapy expectations of the patient;
- Establishing understanding of the symptoms, available treatments and prognosis, conveying a "biopsychosocial disease model" in order to relieve the patient of feelings of guilt, self-reproach and feelings of failure;
- Evaluation of current conflicts in life, unburden the patient of excessive obligations and demands in job and family;
- Aversion of depression-related wishes to hastily rearrange the life; support in defining and reaching concrete, realistic goals in order to feel successful again (positive intensification);

- Helping the patient to appreciate that adequate therapies are necessary (eg, antidepressants, guideline-oriented psychotherapy).
- Involvement of relatives, strengthening of resources;
- Addressing suicidal impulses, being prepared manage a crisis.

Among the psychotherapeutic procedures available in Germany for **outpatient treatment** of depressive disorders, those financed by mandatory health insurance (gesetzliche Krankenversicherung, "GKV") are **behavioural therapy** and **analytical and other psychodynamic psychotherapies** (designated guideline-oriented procedures, "Richtlinienv erfahren"). Other procedures are not reimbursed by outpatient GKV, eg, **interpersonal psychotherapy** or **client-centred psychotherapy**. Guideline-oriented psychotherapy concepts generally implicate a comprehensive treatment strategy, including the elimination of symptoms, stabilization of improvements, and relapse prophylaxis.

In **inpatient care**, various psychotherapy procedures are used: *psychodynamic, modified analytic, behavioural therapeutic, client-centred therapeutic and systemic (family-) therapeutic, or interpersonal psychotherapy*. These are supplemented by further methods that are influenced by psychotherapy, eg, *psychoeducation, occupational therapy, groups for relatives, music-, art- and design therapy, or relaxation techniques and body- and movement-oriented therapies*.

Psychotherapeutic monotherapy is justified the most in *mild and moderate depressive disorders*. In *moderately severe to severe depressive episodes*, a differential indication is necessary. In *severe depressive episodes*, the delayed onset of effect of sole psychotherapy must be considered compared to sole pharmacotherapy or a combination of pharmaco- and psychotherapy. Analogous to pharmacotherapy, the initiation of psychotherapy specific to the disorder may be deferred in *mild depression*, if the depressive symptoms can be expected to resolve without therapy. Still, the symptoms should be re-evaluated within the next two weeks ("**watchful waiting**") and the initiation of a specific therapy be considered (see also "Algorithm for the therapy of depression").

Recommendation/Statement	Grade of recommendation
3-38 Working towards a stable therapeutic relationship is crucial for the quality and success of every psychotherapeutic intervention.	B

3.4.1 Recommendations in psychotherapeutic acute treatment

Recommendation/Statement	Grade of recommendation
3-39 In mild depression, the initiation of psychotherapy specific to the disorder may be deferred, if the depressive symptoms can be expected to resolve without therapy ("watchful waiting"). If the symptoms remain or worsen after 14 days, the option of a specific therapy should be discussed with the patient.	0
3-40 For the treatment of acute mild to moderate depressive episodes, psychotherapy should be offered.	A
3-41 In acute severe depression, a combination of pharmaco- and psychotherapy should be offered.	A
3-42 If only a monotherapy is being considered, outpatients with acute moderate to severe depressive episodes should be offered psychotherapy alone as equivalent to a pharmacotherapy.	A
3-43 Depressive patients with psychotic symptoms should always receive drug therapy.	Statement

3.4.2 Recommendations in the psychotherapy of dysthymia, double depression and chronic depression

Only relatively few clinical studies investigate psychotherapy in patients with dysthymia, double depression and chronic depression. Sample sizes were low in these studies and the duration of treatment short. The study results show that psychotherapy is also effective in chronic depression, but combination treatment with antidepressants and psychotherapy is superior.

Recommendation/Statement	Grade of recommendation
3-44 Patients with dysthymia, double depression or chronic depression should be advised that combination treatment with antidepressants and psychotherapy is more effective than monotherapy.	A

3.4.3 Combination of antidepressants and psychotherapy

In clinical practice, psychotherapy is often combined with pharmacotherapy in the treatment of depression. This can be differentiated into three different forms:

1. Psychotherapy is initiated after pharmacotherapy in the acute phase of treatment.
2. The other type of treatment is added if one treatment alone is not or only slightly effective (augmentation) or if other new aspects justify the specific indication of pharmacotherapy or psychotherapy.
3. Both types of treatment are used simultaneously.

Recommendation/Statement	Grade of recommendation
3-45 In severe, recurrent or chronic depression, dysthymia and double depression, it should be determined whether a combination of pharmacotherapy and psychotherapy is more appropriate than psychotherapy or pharmacotherapy alone.	B
3-46 Clinical studies provide evidence that compliance to drug therapies is higher, if psychotherapy is performed at the same time.	Statement

3.4.4 Maintenance therapy and relapse prophylaxis through psychotherapy

Because depressive disorders are often recurrent, measures are necessary to maintain a successful therapy and prevent relapses. Psychotherapeutic strategies are of growing importance, as they help to maintain treatment success. In addition, adequate procedures for the treatment of residual symptoms in partial remission are useful.

3.4.4.1 Psychotherapy as single maintenance therapy / relapse prophylaxis

Recommendation/Statement	Grade of recommendation
3-47 In order to maintain the therapy benefits and decrease the risk of relapse, adequate psychotherapeutic after treatment (maintenance therapy) should be offered following the acute therapy .	A

3.4.4.2 Psychotherapy as part of combination treatment

Recommendation/Statement	Grade of recommendation
3-48 Longer-term stabilizing psychotherapy (recurrence prophylaxis) should be offered to patients with increased risk of a relapse.	A

3.4.5 Effectiveness of psychotherapy in treatment-resistant depression

Depressive disorders are considered treatment-resistant if the patient shows no response to at least two adequately (up-)titrated antidepressants of different classes.

Recommendation/Statement	Grade of recommendation
3-49 Patients with therapy-resistant depression should be offered an appropriate psychotherapy.	B

3.5 Non-medicamentous somatic therapies

3.5.1 Electroconvulsive therapy

Electroconvulsive therapy (ECT) works by inducing generalized seizures via brief electric stimulations of the brain while under general anaesthesia in combination with muscle relaxants. ECT is a safe treatment with extremely low mortality- and morbidity rates. The **relapse rates without maintenance therapy after ECT is high**: In 50% to 95% of the patients relapsing after ECT, the relapse occurs within 6 months.

Recommendation/Statement	Grade of recommendation
3-50 EKT should be considered as an alternative treatment in severe, therapy-resistant episodes.	A
3-51 EKT may also be used in maintenance therapy in patients who <ul style="list-style-type: none"> • responded to EKT during a depressive episode; • did not respond to another guideline-oriented antidepressive therapy; • show psychotic traits or • prefer EKT. 	0

3.5.2 Sleep deprivation therapy

Partial deprivation of sleep in the second half of the night or, if appropriate, **complete deprivation of sleep**, is the only antidepressive intervention leading to pronounced and evident improvements on the same day. Because sleep restriction therapy is easy to carry out in outpatient and inpatient settings, non-invasive, cost-efficient and fast-acting, it can be added to existing antidepressive therapy, especially, if a rapid response is necessary or if drug therapy is insufficient and augmentation with sleep restriction therapy is intended. The antidepressive effect, though, is generally not sustained.

Recommendation/Statement	Grade of recommendation
3-52 Treatment of depressive episodes with sleep restriction therapy should be considered, if a short-acting albeit short-lasting response is intended or another guideline-oriented treatment is supplemented.	B

3.5.3 Light therapy

Seasonal affective disorder (*seasonal affective disorder* per F33) is a *subtype of recurrent depressive disorders* following a seasonal pattern. "Winter"-depression is the most common type of seasonal depression in which patients are showing symptoms of a clinical depression in particular in autumn or winter and recover completely in spring and summer. **Light therapy** or **SSRI** are first-line treatments in seasonal depression.

Recommendation/Statement	Grade of recommendation
3-53 Light should be considered in patients with recurrent, seasonally associated mild to moderate depressive episodes.	A
3-54 Patients with a season-dependant depressive episode who respond to light therapy may continue light therapy throughout the winter.	O

3.5.4 Physical exercise

Recommendation/Statement	Grade of recommendation
3-55 Based on clinical experience, physical exercise can be recommended to increase well-being and relieve depressive symptoms.	CCP

3.5.5 Newer, non-pharmacological therapeutic options

3.5.5.1 Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a new, non-invasive method to stimulate cortical neurons by magnetic induction. It uses a short, highly intensive magnetic field to repetitively (daily for two weeks) stimulate the left or right prefrontal cortex.

Recommendation/Statement	Grade of recommendation
3-56 Clinical evidence is too limited to give any recommendations to general clinical usefulness and applicability of repetitive transcranial magnetic stimulation (rTMS) and vagus nerve stimulation, which are new somatic therapies for depression.	Statement

3.5.6 Supportive therapies und therapeutic measures

Occupational therapy aims to restore and maintain functioning, participation and quality of life in important, individually different areas (eg, self-care, house keeping, economic independence, job and education).

Sociotherapy offers chronically mentally ill patients support and ways to manage disease-specific deficits and the resulting social barriers. Without help seriously depressive patients are often not able to claim the benefits to which they are entitled. Sociotherapy works to enable them to claim medical and prescribed benefits. It is meant to help the patient reduce psychosocial deficits through motivation and structured training measures; the patient should be enabled to accept required benefits and claim them independently.

Psychiatric home-care is offered by the community. It is a supportive measure to allow mentally ill patients to live dignified, independent lives within familiar social networks. Home-care is intended to involve the people in the environment and provide social integration. Psychiatric home care is an integral part of the concept of "home treatment", which allows the treatment even of the seriously ill, in domestic settings. Outpatient psychiatric care may avoid recurrent hospitalizations, which are often perceived as stigmatizing by affected people and their environment. By offering flexibility and home visiting, outpatient care aims to prevent therapy discontinuations. It serves to empower the patient in coping with the disease and learning about measures to prevent a relapse.

3.6 Therapy in comorbidity

In clinical practice, comorbidity is the rule and means the coexistence of two or more different diseases. Lifetime comorbidity is the coexistence of two or more different diseases throughout the life of an individual.

3.6.1 Depression and comorbid mental disorders

The comorbidity of mental disorders may substantially complicate the course of disease and make treatment difficult or lead to therapy resistance. Thus, accurate differential diagnostics is especially important in depressive disorders.

3.6.1.1 Anxiety disorder and obsessive-compulsive disorder

The comorbidity of depressive and anxiety disorders involves increased symptom intensity, chronicity, aggravated functional disabilities and increased suffering, a **weaker response** to antidepressive pharmaco- and psychotherapeutic monotherapy and **increased suicidality**.

Recommendation/Statement	Grade of recommendation
3-57 The comorbidity of depressive and anxiety disorders can be effectively treated by both psychotherapy (empirical evidence for cognitive behavioural therapy [CBT], interpersonal therapy [IPT]), and pharmacotherapy (empirical evidence for SSRI and Venlafaxine).	Statement

3.6.1.2 Alcohol dependence

About one third of the patients with affective disorders report **substance abuse** during their lifetime. About one quarter of all male alcoholics and half of all female alcoholics develop depression. This is especially important, since both depression and addictive disorders are associated with increased suicidality.

Recommendation/Statement	Grade of recommendation
3-58 In the comorbidity of alcohol dependence and depressive disorder, pharmacotherapy with antidepressants (empirical evidence for fluoxetine, desipramine and mirtazapine) reduces both depressive symptoms and the risk of alcohol-related relapse.	Statement
3-59 In the comorbidity of alcohol dependence and depressive disorder, antidepressive psychotherapy reduces depressive symptoms, either as monotherapy or part of combination treatment with pharmacotherapy or alcohol-specific psychotherapy (empirical evidence for CBT).	Statement
3-60 In the comorbidity of alcohol dependence and depressive disorder, the treatment of depression, independently of any crisis intervention, should only be initiated after 2-4 weeks of alcohol abstinence, because only then it is possible to make a valid diagnosis and indication. In acute situations (eg, severe depressive episode or existing suicidality) action must be taken immediately.	B

3.6.1.3 Eating disorders

According to some studies, the lifetime prevalence of a **comorbid depression** is about 75% among individuals with **eating disorders**.

Recommendation/Statement	Grade of recommendation
3-61 There are no systematic studies of comorbid depression in eating disorders. Thus, no evidence-based recommendations can be given except those specific to the treatment of eating disorders and depression, respectively.	Statement
3-62 In the comorbidity of a depressive episode and bulimia nervosa, pharmacotherapy with fluoxetine may be offered to improve the depressive symptoms.	Statement
3-63 The pharmacotherapy of depression in eating disorders should take into account substance-specific effects on the individual eating disorder, eg,	Statement

weight gain under mirtazapine, mianserine and sedating tricyclic antidepressants, nausea and reduction of appetite under SSRI. There is empirical evidence that fluoxetine may reduce eating attacks.	
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The effect of antidepressants may be reduced, especially in malnutrition and low body weight.

3.6.1.4 Personality disorders

Depressive disorders and **personality disorders** coexist in 30-40 % of the patients, according to clinical samples. In this analysis, the most frequently reported comorbid personality disorders were *anxious [avoidant], borderline, and paranoid personality disorders*.

Recommendation/Statement	Grade of recommendation
3-64 There is empirical evidence for the efficacy of pharmacotherapy with an SSRI or MAO-inhibitor or an atypical antipsychotic in patients with comorbidity of a depressive disorder and borderline personality disorder.	Statement
3-65 There is empirical evidence that psychotherapy (cognitive behavioural therapy [CBT], interpersonal therapy [IPT] and psychodynamic short-term psychotherapy) is effective in patients with the comorbidity of a depressive disorder and a personality disorder (borderline, paranoid, anxious [avoidant] and dependent), either as monotherapy or in combination with pharmacotherapy. Furthermore there are indications that the combination of psychotherapy and pharmacotherapy is more effective than pharmacotherapy alone in the comorbidity mentioned above.	Statement

3.6.1.5 Somatoform disorders

Following the International Classification of Diseases (ICD-10) the category **somatoform disorders** contains *somatisation disorder, somatoform autonomic dysfunction, persistent somatoform pain disorder, dissociative (conversion) disorder, hypochondriacal disorder, dysmorphophobia*. In clinical samples, somatoform disorder and comorbid depressive disorder occurred with a prevalence of between 50 % and 90 % in inpatients.

Recommendation/Statement	Grade of recommendation
3-66 Although depressive disorders and somatoform disorders frequently occur together, due to insufficient clinical evidence no recommendations can be given on the pharmaco- and psychotherapy in this comorbidity. Accordingly, the evidence-based treatment recommendations for the two individual disorders apply, eg, the guideline "somatoform disorders".	Statement

3.6.2 Depression and comorbid somatic diseases

Depression and somatic diseases occur together frequently. The lifetime-prevalence of a depressive or anxiety disorder in somatically ill individuals is about 40%. Neurological, endocrine and cardiovascular diseases as well as malignancies are frequently complicated by depressive disorders. The coexistence of a depressive disorder may predispose to the intensification of somatic symptoms, poor adaptation to the disease, reduced treatment adherence and increased psychosocial disability.

Recommendation/Statement	Grade of recommendation
3-67 Due to insufficient clinical evidence, only limited specific recommendations can be given on the effectiveness of psychotherapy in the comorbidity of depressive disorders and somatic diseases.	Statement
3-68 Pharmacotherapy (empirical evidence for SSRI, TCA) is effective in reducing depressive symptoms in the comorbidity of depressive disorders and somatic diseases.	Statement

3.6.2.1 Cardiovascular diseases and stroke

A *depressive disorder* is considered a risk factor for both the *development of coronary heart disease (CHD)* and *mortality*. Drug treatments need to be tested for cardiac tolerability and possible side-effects in CHD patients.

Recommendation/Statement	Grade of recommendation
3-69 In the comorbidity of coronary heart disease and a moderate to severe depressive disorder, pharmacotherapy should be offered preferentially with sertraline or citalopram.	A
3-70 In coronary heart disease and comorbid depressive disorder, tricyclic antidepressants should not be prescribed due to their cardiac adverse effects.	A
3-71 Currently, no clear recommendations can be given on the use of psychotherapy in depressive disorders and comorbid heart disease.	Statement
3-72 Patients with depression after a stroke should be offered pharmacotherapy taking into account the risks of anticholinergic side-effects (empirical evidence for fluoxetine, citalopram and nortriptyline).	B

3.6.2.2 Cancer

Cancer and its treatment often impact the mental well-being. Medical treatments and the disease itself lead to functional stress and dysfunction in different areas. Furthermore the disease affects partnership and family. Dependent on service area, tumour type, severity and gender, 30-40 % of patients with cancer manifest comorbid mental disorders within the last twelve months.

Recommendation/Statement	Grade of recommendation
3-73 In the comorbidity of a moderate to severe depressive disorder and cancer, pharmacotherapy may be offered with an antidepressant, especially a SSRI.	0
3-74 Specific studies on the psychotherapy of depression in cancer and comorbid depressive disorders are limited. Therefore it is only possible to refer to general recommendations on psychotherapy.	Statement

3.6.2.3 Diabetes mellitus

The prevalence of depressive disorders in patients with diabetes mellitus is up to 30 % and twice as high as that in persons with healthy metabolism. In up to 75 % of patients with diabetes and comorbid depression the course is chronic, ie, characterized by *recurrent depressive episodes*. Depression is associated with *reduced metabolic control or complications*.

Recommendation/Statement	Grade of recommendation
3-75 In the pharmacotherapy of depression in diabetes mellitus, substance-specific effects on diabetes should be taken into account, eg, reduced insulin demand with SSRI or gain of weight under mirtazapine, mianserine and sedating tricyclic antidepressants	B
3-76 If pharmacotherapy is planned in the comorbidity of diabetes mellitus and a depressive disorder, SSRI should be offered.	B
3-77 In the comorbidity of diabetes mellitus with diabetic sensorimotor painful neuropathy and a depressive disorder, pharmacotherapy with a tricyclic antidepressant or duloxetine may be offered, because of their analgesic effects. However, gain of weight and worsening of glycaemic control may be associated with TCA.	0

3-78 In the comorbidity of diabetes mellitus and a depressive disorder psychotherapy should be offered to reduce depression and improve general functioning.	B
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3.6.2.4 Chronic pain

Depression is especially common among patients with chronic pain where comorbidity rates are estimated to be up to 70 %. Intensity and duration of chronic pain are directly proportional to the intensity of the depression.

Recommendation/Statement	Grade of recommendation
3-79 If pharmacotherapy of the depression is initiated with comorbid chronic pain, tricyclic antidepressants (amitriptyline, imipramine, desipramine and clomipramine) should be offered preferentially because of their analgesic effects.	B
3-80 Psychotherapy may be offered to patients with depressive disorder and comorbid chronic pain to reduce their depressive symptoms (empirical evidence for CBT and IPT).	O

3.6.2.5 Dementia and Parkinson's disease

Frequency estimates for **depressive symptoms and syndromes** in **dementia** vary widely. The frequencies of the different intensities appear to be similar (*very few depressive symptoms*: 51 %, *mild*: 27 %, *moderate to severe*: 22 %). Dementia patients with a history of depression or family predisposition are at maximal risk to develop depression. Depression is relatively common in *vascular* and *neurodegenerating brain diseases* that affect *subcortical circuits*; prevalence may be as high as 50 %. This is especially true for *Parkinson's disease* and *vascular dementia* or *depression after stroke*.

Recommendation/Statement	Grade of recommendation
3-81 Clinical evidence is insufficient to support specific recommendations on the treatment of depression in comorbidity with dementia.	Statement
3-82 The anticholinergic potential of the drug and consequently the potency to induce a delirium and further worsening of the cognitive function must be considered when choosing the right antidepressant in the comorbidity of dementia and a depressive disorder.	B

3.7 Managing suicidal risk

3.7.1 Suicide risk factors

Suicidality is understood to include all perceptions and behaviours that consciously, actively or through passivity or indifference seek death, or accept death as a possible consequence of an act.

Recommendation/Statement	Grade of recommendation
3-83 Suicidality should always be addressed directly in depressive patients, should be questioned precisely and in detail and should be evaluated in the context of available resources.	CCP

Table 9: Risk factors for suicidality

Suicidal intentions

- Previous suicide attempts (most important risk factor!)
- Pressing thoughts, concrete plans or preparation for suicide
- Violent method
- No dissociation from suicidal ideas/attempts after a long conversation
- Preparations to say goodbye
- Arrangement of suicide

Present clinical symptoms

- Feelings of strong hopelessness, helplessness, worthlessness, guilt
- No concept of future
- Strong constriction to the suicide (presuicidal syndrom), strong pressure to act
- Increasing social isolation, saying goodbye to others, giving away valuables, last arrangements (testament, insurance policies, documents)
- Open and hidden signalization of suicide
- Patient reacts irritated, aggressively, agitatedly, fearfully or in panic
- Altruistic (pseudo-altruistic) ideas of suicide
- Ideas of self-sacrifice
- Ideas of extended suicidality (eg, involvement of partner or children)
- Depressive mania or other psychotic depression (risk of a suicidal raptus)
- Persistent insomnia, anhedonia, loss of weight and poor ability to concentrate
- Substance abuse, dependence

General factors

- Male gender, older age (especially men >70 years)
- Family history of suicidal behaviour
- Personal circumstances: single, unemployed, chronic somatic disease, multiple current burdens and hurts present
- Concurrent suicides in the surroundings
- No religious or similar attachments

3.7.2 Suicide prevention and emergency suicide interventions

Table 10: Main aspects of suicide prevention

1. Dialogue and contact offers;
2. Diagnosis of suicidality including risk factors;
3. Clarification and management of the present situation
4. Therapy planning taking into account the suicidal risk

3.7.2.1 Dialogue and contact offers

The following is relevant when offering a dialogue and contact to a suicidal patient:

- Make space and time available (offer of care);
- Assure emotional accessibility and responsiveness of the patient;
- Reassure the patient that help is possible;
- Address suicide openly and directly, taking the patient seriously;
- De-dramatization and avoidance of trivialization;

- Ask about suicide-preventing bonds, eg, the external (eg, family, children, religious attachment etc.) and internal factors (eg, hope for help, previous experiences, confidence); the more binding factors that are named, the more reasons the patient gives to live, the less likely the patient is to actually commit suicide;
- Convey hope, help and opportunities for change (future-oriented) as well as the offer of continuation of therapy (self or by referral) and plan appropriately;
- Make concrete arrangements for regular, further contact (directly or by phone, including time and place) and define the setting (outpatient/inpatient).

Recommendation/Statement	Grade of recommendation
3-84 Special care and attention must be given to suicidal patients, in terms of increasing the expenditure of time and therapeutic commitment. The concrete care plan depends on individual risk factors, the reliability of the patient, and environmental factors.	CCP

3.7.2.2 Diagnosis of suicidality

Recommendation/Statement	Grade of recommendation
3-85 The diagnostics of suicidal patients includes grading the extent of suicidal tendencies and estimation of the current need for action or rather distance to the suicidality.	Statement

3.7.2.3 Crisis management

The clarification and management of the current crisis situation includes:

- Establishment of a stable relationship, identifying the current reason and need for psycho-pharmaceutical therapies;
- Permitting grief, anger, and fear;
- Recognition of suicide risk, eg, in currently active conflicts (eg, serious partnership problems) or in psychopathological context (severe depressive state, manic symptoms, severe hopelessness);
- Assuring "protective care": avoidance of being alone, inclusion of positively-associated significant others and cultivation of relationships to people serving as constant companion through the crisis in terms of "communication and control", and, if needed, cooperation with appropriate mental health services for suicidal patients;
- Identifying the adequate treatment setting (outpatient, with outpatient psychiatric care if needed, partially inpatient or inpatient; hospitalization voluntarily/ involuntary commitment order; arrangement of indicated medical care);
- in attempted suicide, consultation of a qualified specialist after internal/surgical primary care
- Investigation and planning of further options to provide help;
- Psychotherapy-oriented crisis intervention: immediate start (dialogue/relationship), identification of the reason/trigger;
- Teaming up with the patient against angst, fear of loss, feelings of helplessness, etc.

3.7.2.4 Therapy planning after the acute situation

Specific therapy planning based on the depressive disorder, suicidality, and possible comorbid mental disorders involves the following points:

- Clarification and discussion of further therapy (inpatient or outpatient);
- Treatment of the underlying disorder (mental disorder/crisis; here depressive disorder) according to the appropriate standards of care regarding core psychopharmacotherapy, and psychotherapeutic treatment;
- Planning and initiation of psychopharmacotherapy and/or psychotherapy under consideration of suicidality.

3.7.3 Indications for inpatient therapy

Recommendation/Statement	Grade of recommendation
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3-86 Hospitalization should be considered in patients, <ul style="list-style-type: none"> • who are at acute suicidal risk; • who need medical care after a suicide attempt; • who need intensive psychiatric or psychotherapeutic treatment due to their underlying depressive disorder; • if no sufficiently reliable estimation can be made regarding the persistence of suicidality otherwise, or • if a stable therapeutic relationship cannot be established and the person remains at acute suicidal risk despite initial treatment. 	B
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If the patient is at risk of suicide and does not want to be treated, hospitalization against the will of the patient must be considered.

3.7.4 Pharmacotherapy

3.7.4.1 Antidepressants

Although it would seem logical to assume that drugs acting as antidepressant may also reduce suicidality, this could not be proven for antidepressants.

Recommendation/Statement	Grade of recommendation
3-87 Antidepressants should not be used in the specific treatment of acute suicidality.	B
3-88 Antidepressants may still be used in suicidal patients to treat their depression in line with the general recommendations.	0
3-89 In suicidal patients, antidepressants should be chosen according to their risk-benefit ratio (drugs with lethality at high dose, increased agitation in the early phase).	CCP

3.7.4.2 Mood stabilizer

Recommendation/Statement	Grade of recommendation
3-90 For relapse prophylaxis in suicidal patients, a medication with lithium should be considered to reduce suicidal acts (suicide attempts and suicide).	A

3.7.4.3 Other substances

Because antidepressants (especially SSRI) are thought to potentially trigger suicidality by increasing restlessness, acathisia, and excitatory effects, a combination of **anxiolytic** and **hypnotic drugs** is often recommended, at least in the acute phase up to the onset of effect. Here **benzodiazepines** are relaxing in the short term, calming, anxiolytic, soporific and emotionally dissociative, and suppress depressive and psychotic experiences.

Recommendation/Statement	Grade of recommendation
3-91 Acute treatment (as far as possible <14 days) with benzodiazepine may be considered in patients at suicidal risk.	0
3-92 In suicidal patients experiencing a depressive episode with psychotic traits, the antidepressant should be supplemented by an antipsychotic.	B

3.7.5 Crisis intervention and specific psychotherapies

Generally, the main strategy in acute suicidality to allow a further more cause-oriented follow-on treatment is initial support and relief until the acute self-endangerment subsides. Suicidality requires

an *attentive, empathic* and *direct attitude* from the treating clinician and the *readiness to get involved with the patient without time pressure*.

Recommendation/Statement	Grade of recommendation
3-93 The short-term goal of crisis intervention or psychotherapy in acute suicidality is intensive contact and active, immediate support and relief until the crisis subsides. A stable therapeutic relationship may per se help prevent a suicide.	Statement
3-94 In suicidal patients experiencing a depressive episode, psychotherapy, initially with focus on suicidality, should be considered.	B

3.7.6 Suicide prevention by follow-up care and contact offers

The following steps are thought to be reasonable in patients who (a) were hospitalized due to suicidality and are to be discharged or (b) who were not hospitalized, although they show suicidal behaviour or increased risk of suicidal behaviour:

- Make fixed personal (preferred) or over-the-phone appointments for the first days after discharge.
- Involvement of family or other supportive persons in the planning of the discharge;
- Involvement in the discharge of those continuing the treatment professionally, at least by verbal reporting to them before discharge;
- Complete report to the general practitioner or specialist who continues the treatment immediately after the discharge (diagnostics, previous therapy and discharge);
- If hospitalization is deferred despite increased risk of suicidal behaviour: detailed notes in writing, why the patient was not hospitalized and what agreements were made on further treatment.

Recommendation/Statement	Grade of recommendation
3-95 Follow-up treatment of patients, who were hospitalized due to suicidality, should be planned in the short run, at most 1 week after discharge, because the risk of further suicidal acts is maximal after discharge.	A
3-96 Patients who were hospitalized due to suicidality and did not keep a follow-up appointment after discharge, must be contacted directly to evaluate the risk of suicide or self-harm.	A

Appendices

Appendix 1: Antidepressants classified by substance group

Drug (substance group)	Dosing		Plasma level	Therapeutic drug monitoring (TDM)
	Initial dose (mg/day)	Standard dose (mg/day)	Serum concentration (ng/ml)	Correlation of serum level and efficacy
Tri- and tetracyclic antidepressants (TCA) – nonselective monoamine-reuptake inhibitors (NSMRI)				
Amitriptyline	25-50	100-300	80-200	very strong
Amitriptylinoxide	30-60	100-300	--	--
Clomipramine	25-50	100-250	175-450	very strong
Desipramine	25-50	100-250	100-300	strong
Doxepine	25-50	100-300	50-150	demonstrated
Imipramine	25-50	100-300	175-300	very strong
Maprotiline	25-50	100-225	125-200	demonstrated
Nortriptyline	25-50	50-200	70-170	very strong
Trimipramine	25-50	100-300	150-350	demonstrated
Selective serotonin-reuptake inhibitors (SSRI)				
Citalopram	20	20-40	30-130	demonstrated
Escitalopram	10	10-20	15-89	limited
Fluoxetine	20	20-40	120-300	demonstrated
Fluvoxamine	50	100-250	150-300	limited
Paroxetine	20	20-40	70-120	demonstrated
Sertraline	50	50-100	10-50	demonstrated
Monoamine oxidase (MAO) inhibitors				
Moclobemide	150	300-600	300-1000	limited
Tranylcypromine	10	20-40	--	not proven
Selective serotonin-/noradrenalin-reuptake inhibitors (SSNRI)				
Vanlafaxine	37.5-75	75-225	195-400	strong
Duloxetine	30-60	60	20-100	
Selective noradrenalin-reuptake inhibitors (SNRI)				
Reboxetine	4-8	8-12	10-100	limited
Alpha2-receptor antagonists				
Mianserine	30	60-120	15-70	demonstrated
Mirtazapine	15	15-45	40-80	demonstrated
Selective noradrenalin- and dopamine-reuptake inhibitors				
Bupropione	150	150-300	up to 100	limited
Melatonin-receptor agonist and serotonin 5-HT_{2C}-receptor antagonist				
Agomelatine	25	25-50	No data	not recommended due to very short half-life

Appendix 2: Other drugs in the treatment of depression

Drug (substance group)	Dosing		Plasma level	Therapeutic drug monitoring (TDM)
	Initial dose (mg/day)	Standard dose (mg/day)	Serum concentration (ng/ml)	Correlation of serum level and efficacy
Unclassified antidepressants				
Trazodone	50-100	200-400	650-1500	demonstrated
Lithium salts	Dose exclusively according to plasma levels. Usual starting dose: 8-12 mmol/day	Target level: 0.6-0.8 mmol/l	very high	--
Phytopharmaceuticals				
Hypericum perforatum (St.John's Wort)	Mechanism of action and active compound unclear. Dosing unclear because of variations in the substance concentrations of the herbal formulation.			
	Marketed: 500-1000 mg dry extract			

Appendix 3: Evidence levels and grades of recommendation

S3-guidelines of the AWMF and NVL aim at providing recommendations **based on best available evidence and the consensus of all contributors**. This evidence-based approach implies that a priori the best available evidence is established for various questions and then classified according to methodological criteria. The most reliable results for efficacy testing of medical or psychotherapeutic interventions are generally obtained from randomized controlled trials (RCT), because they minimize the uncertainty (chance, bias), provided they are conducted methodologically sound and appropriate to the study objective.

The lack of RCTs on individual procedures, however, does not indicate a procedure is not efficient. If no RCTs, meta-analyses, or systemic reviews (on the basis of guidelines or literature research) were available on a particular question, controlled, nonrandomized studies were searched, and in the next level correlative or comparative studies or case series. The level of evidence was crucial for determining the recommendation level: the higher the level of evidence, the stronger the recommendation.

Besides evidence, other clinical factors were included in the grading of recommendations, especially:

- Ethical obligations;
- Clinical relevance of the efficacy measures in the study
- Applicability of the study results to the target population;
- Patient preferences and
- Usefulness in daily routine, especially in the different service areas.

Table 11: Levels of evidence

Ia	Evidence from the meta-analysis of at least three randomized controlled trials (RCTs)
Ib	Evidence from at least one randomized controlled study or a meta-analysis of less than three RCTs.
IIa	Evidence from at least one methodologically well controlled study without randomization
IIb	Evidence from at least one methodologically sound, quasi-experimental descriptive study.
III	Evidence from methodologically sound, non-experimental observational studies, eg, comparative studies, correlation studies and case reports.
IV	Evidence from reports of expert committees or expert opinions and/or clinical experience of acknowledged authorities.

According to these consensus aspects **up- and downgrading of the grade of recommendation was possible relative to the evidence level**. In addition to recommendations, the consensus committee adopted also so-called **statements**. These were used to indicate that the experts of the consensus committee have found a procedure useful despite lacking evidence, or to indicate missing evidence and the need for further research. Consensus to all recommendations and statements in this guideline was obtained from a nominal group process.

The following guidelines were used as source:

- “National Clinical Practice Guideline Depression” of the british National Institute of Health and Clinical Excellence;
- “Behandlungsleitlinie Affektive Erkrankungen” of the German Society for Psychiatry, Psychotherapy, and Neurology;
- “Versorgungsleitlinien für depressive Störungen in der ambulanten Praxis” of the German Competence Network Depression, Suicidality;
- „Practice Guideline for the Treatment of Patients With Major Depressive Disorder“ of the American Psychiatric Association;
- „Clinical Guidelines for the Treatment of Depressive Disorders“ of the Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments;
- „Gemeinsame Leitlinien der Deutschen Gesellschaft für Psychotherapeutische Medizin, der Deutschen Gesellschaft für Psychoanalyse, Psychotherapie, Psychosomatik und Tiefenpsychologie, des Deutschen Kollegiums Psychosomatische Medizin und der Allgemeinen Ärztlichen Gesellschaft für Psychotherapie“;
- „Evidenzbasierte Leitlinie zur Psychotherapie Affektiver Störungen“ of the German Society for Psychology;
- Guideline „Empfehlungen zur Therapie der Depression“ of the Drug Commission of the German Medical Association.

Table 12: Grades of recommendation

A	“Do”- recommendation: at least one randomized, controlled study of overall good quality and consistency, directly related to the respective recommendation and not extrapolated (evidence levels Ia and Ib)
B	“Should do”-recommendation: well conducted, but not randomized clinical studies, directly related to the recommendation (evidence levels II or III) or extrapolated from evidence level I, if there is no relation to the specific question.
0	“May do”-recommendation: reports of expert circles or expert opinion and/or clinical experience of acknowledged authorities (evidence category IV) or extrapolation from evidence Levels IIa, IIb or III. This grade indicates that appropriate clinical studies of good quality did not exist or were not available.
CCP*	“Clinical consensus”: recommended in good clinical practice (“good clinical practice point”) as consensus and, based on the clinical experience of the members of the guideline group, as standard in the treatment, where experimental scientific research is not possible or intended.

* Clinical Consensus points (CCP) were introduced divergent to usual NVL-procedures, to account for the special requirements related to the simultaneous preparation of the S3-guideline and the National Disease Management Guidelines (NVL).

In the present guideline the grading of recommendations are **based on evidence categorized according to the British NICE**, which is based on methodological quality and uses the modified categories of the source-guideline. The translation into recommendation levels of the NVL was performed in reference to the actual NVL-methods-report (see <http://www.versorgungsleitlinien.de>) and is shown next.

Table 13: Translation of evidence levels of the S3-guideline into grades of recommendation and symbols of the NVL Unipolar Depression

Evidence level (analogue to NICE)	Source	Grade of recommendation S3/NVL	Symbol NVL	Meaning
I	Meta-analyses; high-quality randomized, controlled studies	A	↑↑↑	Strong recommendation
II or III	Controlled, nonrandomized studies; observational	B	↑	Recommendation

	studies			
IV	Expert opinion	0	↔	Recommendation open
-	Clinical consensus point*	CCP*	-	Good clinical practice*

* Clinical Consensus points (CCP) were introduced divergent to usual NVL-procedures, to account for the special requirements related to the simultaneous preparation of the S3-guideline and the National Disease Management Guidelines.

replaced by Version 5

Appendix 4: Critical methodical aspects

(Source: see long version)

Efficacy assessments in drug therapy mostly use the **Hamilton Rating Scale for Depression (HAMD)**, which is **not an optimal tool**, as basic efficacy measure. Nevertheless, there is a high degree of correlation ($r=0.8$) between the HAMD and other clinically relevant parameters, eg, reported patient complaints. The main advantages of the HAMD are it is easy-of-use and allows worldwide comparison of study results.

Most acute studies are short-lasting (typically six to seven weeks), because study extensions beyond six weeks do not yield basic new insights regarding response and remission rates. Some authors challenged the clinical relevance of the efficacy of antidepressants. They argue that the effect of antidepressants essentially has been biased by unspecific effects, spontaneous improvements or placebo effects, that authors were less likely to publish negative results (publication bias) and that the double-blind design were broken by side-effects of the verum. In a Cochrane review antidepressants (tricyclics) were only marginally superior to active placebos (substances that imitate side-effects). The differences in depression severity at the end of the study were rated as not clinically relevant.

Other authors answered that the high and increasing placebo response rates were due to the **increasing inclusion of patients with mild depression only**. These patients had higher rates of spontaneous improvement and were preferentially included in placebo-controlled studies based on the feasibility of the study and fewer ethical concerns. In studies with severely depressive patients the effects of antidepressants would be more pronounced. They argue furthermore that the increasing tendency to prolong the duration of placebo-controlled studies has contributed to increasing improvement rates under placebo. In addition, **the clear advantage of antidepressants compared to placebo during maintenance therapy**, when the placebo-effect is less relevant, shows the pharmacological efficacy of antidepressants.

The German Institute for Quality and Efficiency in Health Care (IQWiG) systematically evaluates the benefit and the harm of drugs. In their report on bupropion, mirtazapine and reboxetine the institute concludes that the efficacy of reboxetine for the treatment of depression has not been proven. The evaluation of reboxetine was complicated by a long-time refusal of the Pfizer drug company to provide unpublished data. In addition, the systematic meta-analysis of Cipriani et al. compared twelve modern antidepressants and found reboxetine to be last with regard to efficacy and to tolerability. This prompted the German Federal Joint Committee (G-BA) to exclude a reboxetine medication from refund by the statutory health insurance from the 1st of April 2011 on. For self-pay patient reboxetine is still available and approved. Given this, the use of reboxetine is not recommended by this guideline.

The **significance of randomized, clinical trials (RCTs)**, especially for proving of efficacy of psychotherapeutic procedures, has been **discussed controversially** in Germany for some time (eg, in Wissenschaftlicher Beirat Psychotherapie (§11 PsychThG) or in the Unterausschuss Psychotherapie des Gemeinsamen Bundesausschusses). Although it is accepted that RCTs generally produce the most reliable efficacy results for therapeutic methods, the relevance of these data in clinical practice (effectiveness) is considered to be questionable.

Especially the paradigm of randomization in studies is thought to be associated with practical difficulties. In psychotherapy the **match**, ie, the trustful and emotionally stable **relationship between patient and therapist**, and the **patient's preference** for a particular therapeutic approach in daily routine, are very important. Furthermore, because of the **intrinsic difficulties in blinding** psychotherapy, there is no compensation for the **strong allegiance effect** in psychotherapeutic research, ie, the bias on outcomes introduced by the therapeutic orientation of the investigator.

Another problem constitutes the **design of adequate control** in psychotherapeutic interventions. **Control by other psychotherapeutic procedures** is generally much more difficult than in drug interventions due to the higher expenses (recruitment of adequately trained and supervised therapists in a therapy procedure that is not primarily available). Meta-analyses of numerous randomized, controlled trials show that the efficacy of psychotherapy correlates with the "activity" of the control treatment. Thus, the measured efficacy is higher in comparison to a waiting-list group or drug placebo than in comparison to active control by antidepressants or unsystematic, supportive conversation.

There is no statistically significant difference in the efficacy of a psychotherapy between studies using a waiting list or drug placebo as control.

The call for **controlled studies or field studies** that are closer to clinical practice is based on the fact that patients recruited to RCTs are generally treated for notably shorter periods than outpatients in clinical practice in Germany. Also, there is a **lack of studies** that (a) rather investigate the **benefit in daily clinical routine** (effectiveness) than just effects under controlled conditions (efficacy), and (b) plan **sufficient time for treatment and catamnesis** (this is also true for antidepressant research). Consequently, it is useful for the evaluation of the overall benefit of a particular psychotherapeutic procedure to include in addition to randomized, clinical studies other study designs, eg, original case series and health care studies on benefit and harm of a therapy in daily routine. Finally, It has been argued that in clinical practice the majority of patients suffer from various, relevant **comorbidities**, which make a standardized therapy approach difficult.

As opposed to these possible limitations, comprehensive systematic analyses of psychotherapeutic studies **show that RCTs produce valid efficacy outcomes for psychotherapeutic procedures**, ie, they can determine whether the measured effect intrinsically results from the procedure or from other factors. Two complex secondary analyses of meta-analyses found that **laboratory and field studies** show basically **similar effect sizes** (eg, in symptomatic improvements). Finally, it was demonstrated that other therapies may also serve as methodically sound controls in practice.

The consensus group did **not arrive at consistent conclusions** as to whether or not the significance and importance of RCTs in psychotherapeutic research is as high as in the benefit/harm analysis of drugs. The group agreed that the design and conduct of valid RCTs may be more complicated in psychotherapy research (eg, randomization, higher importance of contextual factors, long observation time). This led to discrepancies in the number of RCTs conducted for the various psychotherapeutic procedures. **The absence of RCTs in a particular procedure, though, does not necessarily mean the procedure is not effective.** In guideline-oriented psychotherapeutic health care no distinction is made between acute therapy and maintenance therapy/relapse prophylaxis, due to conceptual reasons (see Chapter H 3.4.6.2 in the long version "Psychotherapie als alleinige Erhaltungstherapie bzw. Rezidivprophylaxe).

As a result of the above discussion, the consensus group decided on a **differentiating approach for rating the recommendations for the Chapter Psychotherapy**:

- No specific recommendation was given for any of the procedures;
- All used procedures of the guideline-oriented psychotherapy were mentioned;
- Existing studies (RCTs and meta-analyses) were quoted for all investigated procedures. If there were no studies on a particular procedure, naturalistic studies were also factored in.

Hereby, it is intended to give the user of the guideline a general idea of available evidence in specific procedures. All participants consented to this approach.

Appendix 5: Organisations responsible for the guideline

PUBLISHER

The Guideline **Unipolar Depression** was initiated and coordinated as S3-Guideline by the **German Association for Psychiatry and Psychotherapy (DGPPN)** and is jointly published as combined S3-Guideline/National Disease Management Guideline

by the participating organizations including the German Medical Association (Bundesärztekammer), National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung), Association of the Scientific Medical Societies, (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften) and the DGPPN.

Responsible organizations

- German Association for Psychiatry and Psychotherapy (Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde [DGPPN]) <http://www.dgppn.de>
In charge for the S3-Guideline
- German Medical Association (Bundesärztekammer [BÄK]) <http://www.baek.de>
- Working Group of the Medical Associations (Arbeitsgemeinschaft der Deutschen Ärztekammern)
- National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung [KBV]) <http://www.kbv.de>
- Association of the Scientific Medical Societies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften [AWMF]) <http://www.awmf-online.de>
- Drug Commission of the German Medical Association (Arzneimittelkommission der deutschen Ärzteschaft [AkDÄ]) <http://www.akdae.de>
- German Chamber of Psychotherapists (conciliary) (Bundespsychotherapeutenkammer [BPtK]) <http://www.bptk.de>
- German Association of the Relatives of Mentally Ill (Bundesverband der Angehörigen psychisch Kranker [BApK]) <http://www.bapk.de>
- German Working Group Self-Help Groups (Deutsche Arbeitsgemeinschaft Selbsthilfegruppen [DAGSHG]) <http://www.dag-selbsthilfegruppen.de>
- German College of General Practitioners and Family Physicians (Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin [DEGAM]) <http://www.degam.de>
- German Society for Psychosomatic Medicine and Medical Psychotherapy (Deutsche Gesellschaft für Psychosomatische Medizin und Ärztliche Psychotherapie [DGPM]) <http://www.dgpm.de>
- German Psychological Society (Deutsche Gesellschaft für Psychologie [DGPs]) <http://www.dgps.de>
- German Society for Rehabilitation Sciences (Deutsche Gesellschaft für Rehabilitationswissenschaften [DGRW]) <http://www.uke.de>

Participated in the consensus process and approved

- German Directors Congress of Psychiatric Hospitals <http://www.bdk-deutschland.de>
- (and Working Group Inpatient Wards)
(Bundesdirektorenkonferenz psychiatrischer Krankenhäuser
(und Arbeitskreis Depressionsstationen)[BDK])

- German Psychologists Association (Berufsverband Deutscher Psychologinnen und Psychologen [BDP]) <http://www.bdp-verband.org>
- German Association of Psychosomatic Medicine and Psychotherapy Specialists (Bundesverband der Fachärzte für Psychosomatische Medizin und Psychotherapie Deutschlands [BPM]) <http://www.bpm-ev.de>
- German Neurologists Association (Berufsverband deutscher Nervenärzte [BVDN]) <http://www.bv-nervenarzt.de>
- German Psychiatrists Association (Berufsverband Deutscher Psychiater [BVDP]) <http://www.bv-psychiater.de>
- German Association of SHI-authorized Psychotherapists (Bundesverband der Vertragspsychotherapeuten [BVVP]) <http://www.bvvp.de>
- Physicians-in-Chief Conference on Psychosomatic-psychotherapeutic Hospitals and Branches (Chefarztkonferenz psychosomatisch-psychotherapeutischer Krankenhäuser und Abteilungen) <http://www.cпка.de>
- German Medical Society for Behavioural Therapy (Deutsche Ärztliche Gesellschaft für Verhaltenstherapie [DÄVT]) <http://www.daevt.de>
- German Association for Psychodynamic Psychotherapy (Deutsche Fachgesellschaft für tiefenpsychologisch fundierte Psychotherapie [DFT]) <http://www.dft-online.de>
- German Psychogeriatric Association (GPA) (Deutsche Gesellschaft für Gerontopsychiatrie und -psychotherapie [DGGPP]) <http://www.dggpp.de>
- German Society for Psychoanalysis, Psychotherapy, Psychosomatics and Depth Psychology (Deutsche Gesellschaft für Psychoanalyse, Psychotherapie, Psychosomatik und Tiefenpsychologie [DGPT]) <http://www.dgpt.de>
- German Society for Behaviour Therapy (Deutsche Gesellschaft für Verhaltenstherapie [DGVt]) <http://www.dgvt.de>
- German Psychoanalytic Society (Deutsche Psychoanalytische Gesellschaft [DPG]) <http://www.dpg-psa.de>
- German Psychoanalytic Association (Deutsche Psychoanalytische Vereinigung [DPV]) <http://www.dpv-psa.de>
- German Psychotherapists Association (Deutsche Psychotherapeutenvereinigung [DPTV]) <http://www.dptv.de>
- German Association for Behavioral Therapy (Deutscher Fachverband für Verhaltenstherapie [DVT]) <http://www.verhaltenstherapie.de>
- German Association of Family Doctors (Deutscher Hausärzteverband) <http://www.hausarzt-bda.de>
- Society for Scientific Client-centred Psychotherapy (Gesellschaft für wissenschaftliche Gesprächspsychotherapie [GwG]) <http://www.hausarzt-bda.org>
- German Research Network on Depression and Suicidality (Kompetenznetz Depression, Suizidalität [KND]) <http://www.kompetenznetz-depression.de>

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