GUIDELINES

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders

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Abstract

Objectives. This 2013 update of the practice guidelines for the biological treatment of unipolar depressive disorders was developed by an international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP). The goal has been to systematically review all available evidence pertaining to the treatment of unipolar depressive disorders, and to produce a series of practice recommendations that are clinically and scientifically meaningful based on the available evidence. The guidelines are intended for use by all physicians seeing and treating patients with these conditions. *Methods.* The 2013 update was conducted by a systematic update literature search and appraisal. All recommendations were approved by the Guidelines Task Force. *Results.* This first part of the guidelines (Part 1) covers disease definition, classification, epidemiology, and course of unipolar depressive disorders, as well as the management of the acute and continuation phase treatment. It is primarily concerned with the biological treatment (including antidepressants, other psychopharmacological medications, electroconvulsive therapy, light therapy, adjunctive and novel therapeutic strategies) of adults. *Conclusions.* To date, there is a variety of evidence-based antidepressant treatment options available. Nevertheless there is still a substantial proportion of patients not achieving full remission. In addition, somatic and psychiatric comorbidities and other special circumstances need to be more thoroughly investigated. Therefore, further high-quality informative randomized controlled trials are urgently needed.

Key words: *Major depressive disorder, acute treatment, continuation treatment, pharmacotherapy, antidepressants*

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Summary

This 2013 update of the practice guidelines for the biological treatment of unipolar depressive disorders was developed by an international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP).

The goal for developing the original guidelines in 2002 and the 2007 version for use in primary care has been to systematically review all available evidence pertaining to the treatment of unipolar depressive disorders, and to produce a series of practice recommendations that are clinically and scientifically meaningful based on the available evidence.

The 2013 update was conducted by a systematic update literature search and appraisal. All recommendations were approved by the Guidelines Task Force.

The guidelines developed are intended for use by all physicians seeing and treating patients with these conditions. This first part of the guidelines (Part 1) covers disease definition, classification, epidemiology, and course of unipolar depressive disorders, as well as the management of the acute and continuation phase treatment. It is primarily concerned with the biological treatment (including antidepressants, other psychopharmacological medications, electroconvulsive therapy, light therapy, adjunctive and novel therapeutic strategies) of adults.

Executive summary of recommendations

General recommendations

For patients who meet diagnostic criteria for depressive episode (ICD-10) or major depressive disorder (DSM-IV-TR), biological treatment (pharmacological and non-pharmacological approaches) should, in general, be considered.

Before treatment starts, a comprehensive treatment plan should be developed on the basis of the patient's history and experience with previous treatments, current clinical subtype, current findings, severity of illness and risk of suicide. Concurrent psychiatric and somatic disorders, non-psychiatric medications, or psychosocial stress factors should be thoroughly considered, as they can contribute to a depressive syndrome or interfere with treatment. Family history for mood disorders and response to treatments should be assessed.

Whichever biological treatment intervention is chosen, psychiatric management should be initiated and continued throughout the treatment. This includes determining treatment plan and setting, establishing, and maintaining a therapeutic alliance, monitoring and reassessing mental status including risk of suicide, reassessing the adequacy of the diagnosis, monitoring the patient's treatment response, side effects and general medical condition, and educating patients and families as to the importance of adhering to treatment.

The ultimate goal of the acute treatment phase is remission. After a period of about 2 weeks of antidepressant treatment, response should be evaluated and if insufficient, optimization strategies should be implemented. At least 8–10 weeks may be required to achieve maximum symptom reduction which is necessary before entering the continuation phase of treatment. The more severe the depression is, the greater the potential benefits are that can be derived from adequate treatment.

The goal of continuation treatment is to prevent a relapse, to eliminate any residual symptoms, and to restore the patient's prior level of psychosocial and occupational functioning.

Maintenance (prophylactic) treatment is aimed at preventing a new episode of depression and suicide (see Part 2 of these guidelines).

Successful treatment of depressed patients with antidepressants includes educating the patients and the families about available treatment options, time to onset of response and noticeable signs of it, early side effects and what to do about them, and the expected course of treatment.

Biological treatment recommendations

Antidepressants are the first-line treatments for a major depressive episode (moderate to severe depressive episode) in the context of Major Depressive Disorder. Depending on individual characteristics and/or patient requests, antidepressant treatment might also be indicated in mild depressive episodes, but, in many such cases, psycho- and sociotherapeutic approaches alone may be sufficient.

Factors to take into account when choosing an antidepressant are: the patient's prior experience with medication (response, tolerability, adverse effects), concurrent medical conditions and use of non-psychiatric drugs, a drug's short- and long-term side effects, toxicity of overdose in patients at risk of suicide, the physician's own experience with the medication, the patient's history of adherence to medication, history of first-degree relatives responding to a medication, patient preferences, potential budgetary constraints, availability of specific antidepressants, and license of compound.

No single class of antidepressants has proven to be more effective or have a more rapid onset than any other, although some tricyclic antidepressants (TCAs) (amitriptyline and clomipramine), and

venlafaxine are slightly more effective than SSRI in severely depressed hospitalized patients. Antidepressants differ considerably in their side-effects profile, potential for interacting with other drugs and in the danger they pose when taken in overdose. Second (e.g., bupropion, maprotiline, mianserin, trazodone) and third (e.g., SSRI, SNRIs, mirtazapine) generation ("newer") antidepressants are generally tolerated better than are the first generation ("older") TCAs, and patients are, thus, less likely to discontinue them. This may have a significant impact on "real-life" efficacy.

In at least 30% of depressive episodes, patients will not respond sufficiently to an adequately performed first-line treatment with any chosen antidepressant. This situation warrants a careful review of the correctness of diagnosis and sufficiency of drug dosing and adherence. Following this, theoretical strategies are: (1) increasing (maximizing) the dose of the initial antidepressant; (2) switching to another antidepressant from a different pharmacological class (e.g., from a SSRI to a TCA or a dual-acting AD); (3) switching to another antidepressant within the same pharmacological class (e.g., from a SSRI to another SSRI); (4) combining two antidepressants from different classes (e.g., an SSRI or a dual-acting AD with e.g., mirtazapine); (5) augmenting the antidepressant with other agents (e.g., lithium, thyroid hormone or atypical antipsychotics) to enhance antidepressant efficacy; (6) combining the antidepressant with a psychotherapeutic intervention; and (7) combining the antidepressant with non-pharmacological biological therapies (e.g., wake therapy, light therapy, ECT). Of these alternatives, augmentation with lithium, quetiapine, and aripiprazole are the best documented strategies at present.

Electroconvulsive therapy (ECT) should be considered as a first-line strategy only in special situations calling for rapid relief from severe depression (e.g., severe psychotic depression, severe depression with psychomotor retardation, "true" treatment-resistant depression, persistent refusal of food, severe suicidality), for patients with previous positive response to ECT and for pregnant women especially during the first trimester.

1. Unipolar depressive disorders

1.1 Introduction

Patients with unipolar depressive disorders present with depressive symptoms. A history of a full hypomanic, manic, or mixed episode is missing, distinguishing them from bipolar affective disorders. Unipolar depressive disorders have been classified into three main diagnostic groups (ICD-10 diagnoses,

World Health Organization 1992; WHO 1992); corresponding DSM-IV diagnoses, American Psychiatric Association, APA 1994), are given in parentheses:

- depressive episode or recurrent depressive disorder (DSM-IV: major depressive disorder (MDD) – single episode or recurrent);
- dysthymia (DSM-IV: dysthymic disorder and other chronic depressive disorders (MDD in incomplete remission and chronic MDD); and
- depressive episode, unspecified, brief recurrent depressions (DSM-IV "subthreshold depressions").

Of these, major depressive disorder (MDD) is, clinically, the most meaningful, given its consequences for patients (e.g., disability and suicide risk) as well as its socioeconomic impact. Subsequently, it has received the most attention in studies. Its treatment – in the acute and continuation phases – is therefore the focus of the recommendations developed in these guidelines. A major depressive episode can be further divided into categories according to its severity (mild, moderate, and severe).

1.2 Goal and target audience of WFSBP guidelines

These WFSBP guidelines provide an update of contemporary knowledge of unipolar depressive disorders and evidence-based recommendations for their treatment. They were developed by the authors and approved by the WFSBP Task Force on Unipolar Depressive Disorders consisting of 50 international researchers and clinicians. The recommendations presented in these guidelines are based on an initial systematic review of all available evidence pertaining to the treatment of unipolar depressive disorders (2002, updated in 2007) and embody important clinical and scientific advancements. The 2013 update was conducted by a systematic update literature search and appraisal.

The guidelines also incorporate the opinions of scientifically respected experts and international representatives of the state-of-the-art treatment of these disorders. In cases where a consensus could not be reached, the authors were mandated to make a final judgment.

The guidelines were originally published in 2002 in two parts Bauer et al. (2002b,c) for use by all physicians, particularly psychiatric specialists (as specified in the Introduction). As with any guideline, the final judgment regarding a particular therapy must be made by the responsible treating physician in light of the clinical picture presented by the patient and the diagnostic and treatment options available.

These guidelines deal primarily with biological (somatic) treatment (e.g., antidepressants). Psychotherapeutic treatment interventions are covered only briefly. The guidelines do not address depressive disorders occurring in bipolar affective disorders (see separate WFSBP guideline, Grunze et al. 2010).

1.3 Methods of literature research and data extraction

The data used for the development of the initial guidelines was collected from the following sources: Agency for Health Care Policy and Research Depression Guidelines Panel (AHCPR 1993); Evidence Report on Treatment of Depression: Newer Pharmacotherapies (AHCPR 1999); American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Revision (APA 2000); British Association for Psychopharmacology Revised Guidelines for Treating Depressive Disorders (Anderson et al. 2000); Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments, Clinical Guidelines for the Treatment of Depressive Disorders (CAN-MAT 2001); Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder (Lam and Levitt 1999); German Association of Psychiatry, Psychotherapy and Psychosomatics (DGPPN 2000), The Cochrane Library; meta-analyses on the efficacy of antidepressant medications identified by a search in the MEDLINE database; major pertinent review articles identified by a search in the MEDLINE database and textbooks, and individual clinical experience of the authors and members of the WFSBP Task Force on Unipolar Depressive Disorders.

For the 2013 update, apart from a systematic update search in the MEDLINE database, the following guidelines published in English were consulted: NICE (2009), APA (2010), CANMAT (2009), SIGN (2010), US Preventive Services Task Force US Preventive Services Task Force (2009), New Zealand Guidelines Group (2008), American College of Physicians (2008), Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression (2004), The expert consensus Guidelines (2001) Alexopoulos et al. (2001), Prevention Practice Committee of the American College of Preventive Medicine (2009), Clinical practice guidelines in the Spanish SHN, ministry of health and consumer affairs (Avalia-t) (Working Group on the Management of Major Depression in Adults 2006), ICSI (2011), Clinical practice recommendations for depression (Malhi et al. 2009), Guideline for the management of late-life depression in primary care (Baldwin et al. 2003) and the German S3-Guideline/National Disease Management Guideline Unipolar Depression (DGPPN et al. 2009).

1.4 Evidence-based classification of recommendations

Each treatment was evaluated based upon the strength of evidence for its efficacy, safety, and feasibility.[1] Given the disparities in medication costs across the world, daily treatment costs were not taken into consideration.

According to Bandelow et al. (2008) and Grunze et al. (2009), six categories of evidence (CE A to F) were used:

CE A: Full evidence from controlled trials
CE B: Limited positive evidence from controlled trials
CE C: Evidence from uncontrolled studies or case reports/expert opinion
CE D: Inconsistent results
CE E: Negative evidence
CE F: Lack of evidence.

See Table I for details.

Recommendations were then derived from the category of evidence for efficacy (CE) and from additional aspects such as safety, tolerability, and interaction potential and where labelled 1 to 5:

RG 1: CE A evidence and good risk–benefit ratio
RG 2: CE A evidence and moderate risk–benefit ratio
RG 3: CE B evidence
RG 4: CE C evidence
RG 5: CE D evidence.

In a number of clinically relevant questions – with no informative external evidence available to answer these questions – recommendations are made, referred to as "Clinical consensus".

1.5 Epidemiology and course of major depressive disorder

Major depressive disorder (MDD) is a severe mood disorder associated with significant morbidity and mortality affecting individuals of all ages and races. The worldwide Global Burden of Disease (GBD) study of the World Health Organization (WHO) has shown variations by country and region but patterns and trends for depressive disorders are remarkably similar worldwide (Murray and Lopez 1997a,b; Üstün et al. 2004; Lopez et al. 2006; Murray et al. 2013; Vos et al. 2013). MDD is characterized by single or recurrent major depressive episodes (MDE). The essential feature of a major depressive episode is a period of at least 2 weeks of depressed mood with abnormalities of neuro-vegetative function

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[1]Note: It is emphasized that a graded efficacy evaluation has its limitations. The strength of a recommendation reflects the scientific evidence on which it is based and not necessarily its importance.

Table I. Categories of Evidence (CE) and Recommendation Grades (RG).

Category of Evidence (CE)		Description
A		*Full evidence from controlled studies*
		is based on:
		2 or more double-blind, parallel-group, randomized controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo" in a study with adequate blinding)
		and
		1 or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists)
		In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least 2 more positive studies or a meta-analysis of all available studies showing superiority to placebo and non-inferiority to an established comparator treatment.
		Studies must fulfill established methodological standards. The decision is based on the primary efficacy measure.
B		*Limited positive evidence from controlled studies*
		is based on:
		1 or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo")
		or
		a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial
		and
		In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least 1 more positive study or a meta-analysis of all available studies showing superiority to placebo or at least one more randomized controlled comparison showing non-inferiority to an established comparator treatment.
C		*Evidence from uncontrolled studies or case reports/Expert opinion*
	C1	*Uncontrolled studies*
		is based on:
		1 or more positive naturalistic open studies (with a minimum of 5 evaluable patients)
		or
		a comparison with a reference drug with a sample size insufficient for a non-inferiority trial
		and
		no negative controlled studies exist
	C2	*Case reports*
		is based on:
		1 or more positive case reports
		and
		no negative controlled studies exist
	C3	Based on the opinion of experts in the field or clinical experience
D		*Inconsistent results*
		Positive RCTs are outweighed by an approximately equal number of negative studies
E		*Negative evidence*
		The majority of RCTs studies or exploratory studies shows non-superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo") or inferiority to comparator treatment
F		*Lack of evidence*
		Adequate studies proving efficacy or non-efficacy are lacking.

Recommendation Grade (RG)	
1	Category A evidence and good risk–benefit ratio
2	Category A evidence and moderate risk–benefit ratio
3	Category B evidence
4	Category C evidence
5	Category D evidence

Bandelow et al. (2008), Grunze et al. (2009).

(appetite, weight loss, sleep disturbances), psycho-motor activity (e.g., loss of energy and interests, agitation, or retardation), cognition (feelings of worthlessness, hopelessness, or inappropriate guilt), as well as anxiety and suicidal ideation (Table II).

Symptoms have to be present most of the day and nearly every day.

MDD has a median lifetime prevalence of 16.1% (range 4.4–18) (Wittchen 2000; Waraich et al. 2004; Wittchen et al. 2011). It occurs in about 5–10% of

Table II. Classification and Criteria of Major Depressive Disorder (DSM-IV) and Depressive Episode (ICD-10).

ICD-10[1] (code)	DSM-IV[2] (code)

A. Depressive episode
  • mild (F32.0): at least 2 typical symptoms, plus at least 2 other common symptoms; none of symptoms intense
  • moderate (F32.1): at least 2 typical symptoms, plus at least 3 other common symptoms; some symptoms marked
  • severe (F32.2): all 3 typical symptoms, plus at least 4 other common symptoms; some symptoms severe with intensity
B. Recurrent depressive disorder (F33): recurrent depressive episodes
	Major depressive disorder
	  A. single episode (296.2×)
	  B. recurrent (296.3×)

Abridged criteria of depressive episode:
Minimum duration of episode: about 2 weeks
 	
Typical symptoms:
1. depressed mood
2. loss of interest and enjoyment
3. reduced energy, increased fatigability
 	
Other common symptoms:
1. reduced concentration and attention
2. reduced self-esteem and self-confidence
3. ideas of guilt and unworthiness
4. agitation or retardation
5. ideas or acts of self-harm or suicide
6. disturbed sleep
7. diminished appetite
	Abridged criteria major depressive episode:
	A. Over the last 2 weeks, 5 of the following features should be present most of the day, or nearly every day (must include 1 or 2):
	  1. depressed mood
	  2. loss of interest or pleasure in almost all activities
	  3. significant weight loss or gain (more than 5% change in 1 month) or an increase or decrease in appetite nearly every day
	  4. insomnia or hypersomnia
	  5. psychomotor agitation or retardation (observable by others)
	  6. fatigue or loss of energy
	  7. feelings of worthlessness or excessive or inappropriate guilt (not merely self reproach about being sick)
	  8. diminished ability to think or concentrate, or indecisiveness (either by subjective account or as observed by others)
	  9. recurrent thoughts of death (not just fear of dying), or recurrent suicidal ideation, or a suicide attempt, or a specific plan for committing suicide
	
	B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
	
	C. The symptoms are not due to a physical/organic factor or illness (e.g., a drug abuse, a medication, a general medical condition)
	
	D. The symptoms are not better explained by bereavement (although this can be complicated by major depression)

[1]0th Revision of the International Classification of Diseases WHO (1992).
[2]4th Revision of the American Psychiatric Association's Diagnostic and Statistics Manual APA (1994).

the adult population during any 1-year period of time, with women at higher risk than men (ratio is approximately 2:1) (Regier et al. 1993; Kessler et al. 1994; Picinelli and Gomez Homen 1997; Ialongo et al. 2004).

At least 10% of all patients presenting in primary care settings suffer from depression (Üstün and Sartorius 1995; Backenstrass et al. 2006), with about 50% presenting with primarily or only somatic symptoms (Fisch 1987). Of all primary care patients with depressive symptomatology, around 25% classify as having MDD, 30% as having minor depression and 45% present with non-specific depressive symptoms. The combined latter two groups could be summarized as "subthreshold" depression (Backenstrass

et al. 2006). Even severely depressed patients are commonly seen first in primary care, as they assume that they are suffering from a somatic illness.

While MDD can begin at any age, even in childhood and adolescence, there are two peaks – in the 20s and 40s (Angst and Preisig 1995; APA 2000). The mean age of onset of MDD has been estimated around the age of 30 (Wittchen 2000).

Untreated, a typical major depressive episode lasts about 6 months or more (Angst and Preisig 1995; Solomon et al. 1997; APA 2000; Wang 2004). Modern pharmacotherapy can alleviate suffering during acute episodes, and placebo-controlled trials show that response and remission occur faster in actively treated groups. MDD is a recurrent disorder and

50–85% of the patients who experience an episode will eventually have another (Keller et al. 1986; Mueller et al. 1999; Kennedy and Paykel 2004; Baghai et al. 2012).

When adequately treated, the prognosis for a depressive episode is good, and most patients return to normal functioning once the episode is over. However, in 20–30% of cases, remission is incomplete, with some depressive symptoms persisting (Angst 1986; Keller et al. 1986; Scott 1988; Paykel 1994; Judd et al. 1998; Bauer et al. 2002b). MDD is associated with considerable morbidity and mortality and, for many, an initial episode of depression evolves into a recurrent and debilitating chronic illness with significant and pervasive impairments in psychosocial functioning (Klerman and Weissman 1992; Mintz et al. 1992; Judd et al. 2000; Hirschfeld et al. 2000; Bromberger 2004; Kennedy and Paykel 2004; Melartin et al. 2004; Papakostas et al. 2004). Studies on the effects of depression on health-related quality of life demonstrate detriments equal to or greater than those for patients with chronic medical illnesses such as ischemic heart disease or diabetes mellitus (Wells et al. 1989; AHCPR 1999; Unutzer et al. 2000). The symptoms in depressive people with co-morbid medical illnesses tend to show less improvement and these patients show a higher relapse rate despite treatment (Iosifescu et al. 2004).

The most serious consequence of MDD is suicide. While the lifetime prevalence of suicide for the general population is less than 0.5%, a meta-analysis showed that the prevalence for patients with affective disorders ranges from 2.2% for mixed inpatient/outpatient populations to 8.6% for those who have been previously hospitalized for suicidality (Bostwick and Pankratz 2000). Depression also substantially increases the risk of death by cardiovascular disease (Wulsin et al. 1999).

The Global Burden of Disease Study estimated that unipolar major depression is the fourth largest contributor to the global burden of disease (premature mortality and disability). With the addition of suicide (not included in the primary tabulations even though most often due to depression), the burden of unipolar major depression increased by nearly 40% (Murray and Lopez 1997b). When defined in terms of years lived with disability (YLD), major depression currently ranks second among all medical causes of disability worldwide (Vos et al. 2013). An update calculation predicts unipolar depression will become first-ranking by the year 2030 (WHO 2004). For more information see Üstün et al. (2004), Lopez et al. (2006), Murray et al. (2013) and Miret et al. (2013).

In addition to the personal suffering of individuals and their families, depression imposes significant costs on society (Brunello et al. 1995; Thase 2001; Fava et al. 2003b; Greenberg et al. 2003; McIntyre and O'Donovan 2004; Sartorius et al. 2007), even more so when not properly diagnosed or under-treated (Wells et al. 1989; Üstün and Sartorius 1995; Unutzer et al. 2000; Young et al. 2001).

1.6 Indications and goals of treatment for major depressive disorder

Antidepressant treatment should be considered for patients who meet diagnostic criteria for depressive episode (ICD-10) or major depressive disorder (DSM-IV) (see Table III). Guidelines differ with respect to the recommendation of antidepressants in mild depressive episodes or depression in primary care. Depending on individual characteristics and/or patient requests, antidepressant treatment might be indicated; otherwise, psycho- and sociotherapeutic approaches alone may be sufficient (Baghai et al. 2011).

Current diagnostic criteria in both classification systems represent a clinical and historical consensus on the most prominent and important symptoms and signs of depressive illness (Table II). Affected individuals present a wide variation of clinical symptoms and signs (Fava and Kendler 2000). It should also be stressed that the clinical syndrome of major depression/depressive episode comprises a heterogeneous group of different types of depression ranging from biologically determined (formerly "endogenous" or "melancholic") conditions to more event-dependent (formerly "reactive") conditions (Freedman et al. 2013). However, in general, it has not been found useful to distinguish between these different types of depression when making (pharmacological) treatment recommendations (Anderson et al. 2000).

Prior to beginning treatment, a comprehensive treatment plan should be developed based on the history of previous treatments, current clinical findings (e.g., the presence of psychotic symptoms, agitation, anxiety, or atypical symptoms), severity of illness, and risk of suicide. Whenever possible, the patient's preferences and previous treatment experiences should be considered. If indicated (e.g., if psychotic features or suicidality co-occurs), the need for inpatient treatment in a specialized facility should be addressed. See Figure 1 for a stepped-care model.

The treatment of major depressive disorder requires conceptualization of acute, intermediate, and long-term goals. Kupfer (1993) have developed a model for the typical course of an MDE including the risk of recurrence and corresponding structured treatment approach. In this model, the three phases of treatment correspond to the three stages of the

Table III. Antidepressants: mode of action and commonly used doses.

Generic Name[1] (in alphabetical order)	Traditional Structural Classification[2]	Classification according to neurochemical action[2]	Starting Dose[3] (mg/day)	Standard Dose[4] (mg/day)	Plasma Levels[5] (Therapeutic range) (ng/mL)
Agomelatine		MT agonist	25	25–50	
Amineptine			100	200–300	
Amitriptyline[6]	TCA		25–50	100–300	80–200*
Amoxapine	TetraCA		50	100–400	
Bupropion[7]		NDRI	150	150–450	
Citalopram[9]		SSRI	20	20–40 (60)	
Clomipramine[8,9]	TCA		25–50	100–250	175–450*
Desipramine	TCA		25–50	100–300	100–300
Dibenzepine	TCA		120–180	240–720	
Doslepine	TCA		75	75–150	
Dothiepin	TCA		25–50	100–300	
Doxepine[9]	TCA		25–50	100–300	
Duloxetine[11]		SNRI	30–60	60–120	
Escitalopram[9]		SSRI	10	10–20	
Fluoxetine[8]		SSRI	20	20–60	
Fluvoxamine[8]		SSRI	50	100–200	
Imipramine	TCA		25–50	100–300	175–300*
Isocarboxazid[9]			20	20–60	
Lofepramine	TCA		70	140–210	
Maprotiline	TetraCA		25–50	150–225	
Mianserin	TetraCA	§	30	60–120	
Milnacipran		SNRI	50–100	100–200	
Mirtazapine		Other$	15	15–45	
Moclobemide		RIMA	150	300–600	
Nefazodone			100	300–600	
Nortriptyline	TCA		25–50	75–200	70–170
Paroxetine[8,9,10]		SSRI	20	20–40 (60)	
Phenelzine[9]		MAOI	15	30–90	
Protriptyline	TCA		10	20–60	
Reboxetine		NARI	4–8	8–12	
Sertraline[8,9,10]		SSRI	50	50–150	
Setiptiline	TetraCA		3	3–6	
Tianeptine		Other#	12.5	25–37.5	
Tranylcypromine[9]		MAOI	10	20–60	
Trazodone			50–100	200–600	
Trimipramine[6,9]	TCA		25–50	100–300	
Venlafaxine[10]		SNRI	37.5–75	75–375	195–400*
Viloxazine			100	200–500	

[1]Availability on the market differs considerably across countries.

[2]*Abbreviations:* MAO-I = irreversible inhibition of monoamine oxidase (MAO); MT agonist = agonist of the melatonine receptor (MT1 und MT2); NARI = noradrenaline reuptake inhibition; NDRI = noradrenaline and dopamine reuptake inhibition; other = other types of receptor or transmitter profile; RIMA = Reversible inhibition of monoamine oxidase A (MAO-A); SNRI = selective serotonine and noradrenaline reuptake inhibitors; SSRI = selective serotonine reuptake inhibitors; TCA = tricyclic antidepressant; TetraCA = tetracyclic antidepressant; § = noradrenaline reuptake inhibion plus presynaptic alpha2-blockade; $ = alpha2-antagonist; # = 5-HT reuptake enhancer.

[3]Lower starting doses may be needed for older adults (>60) or patients with co-morbid medical illness (especially cardiovascular conditions; see text).

[4]Standard doses are generally lower in Japan.

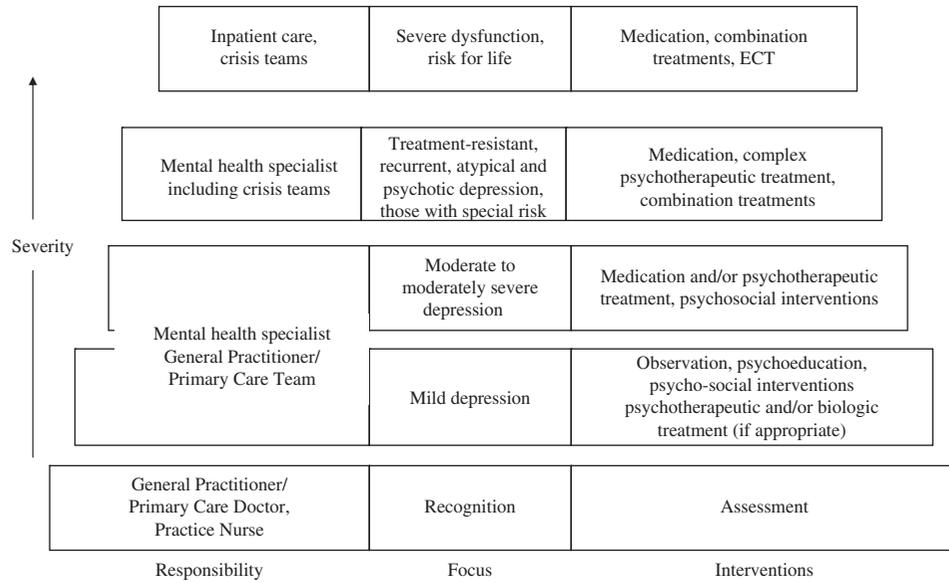[5]Only given for those antidepressants with well established therapeutic range.

Other indications than depression (approved in some countries) or common uses:[6]Chronic pain; [7]smoking cessation; [8]obsessive–compulsive disorder (OCD); [9]anxiety disorders (panic disorders, PTSD, social phobia); [10]generalized anxiety disorder; [11]diabetic and peripheral neuropathic pain, stress urinary incontinence.

*Recommended therapeutic range is the sum of the drug and the active metabolite.

illness: (1) acute therapy, (2) continuation therapy, and (3) maintenance therapy (see Figure 2).

The *acute phase* of therapy is the time period from the initiation of treatment to remission, which is the primary therapeutic goal (Frank et al. 1991; Kupfer 1993). There is consensus that the criteria for remission should involve at least two things. The patient should be asymptomatic (not meet the criteria for

Responsibility	Focus	Interventions
Inpatient care, crisis teams	Severe dysfunction, risk for life	Medication, combination treatments, ECT
Mental health specialist including crisis teams	Treatment-resistant, recurrent, atypical and psychotic depression, those with special risk	Medication, complex psychotherapeutic treatment, combination treatments
Mental health specialist General Practitioner/ Primary Care Team	Moderate to moderately severe depression	Medication and/or psychotherapeutic treatment, psychosocial interventions
	Mild depression	Observation, psychoeducation, psycho-social interventions psychotherapeutic and/or biologic treatment (if appropriate)
General Practitioner/ Primary Care Doctor, Practice Nurse	Recognition	Assessment

Adapted version, original idea from NICE guideline 2004

Figure 1. Stepped-care model.

diagnosis of the disorder and have no or minimal residual symptoms), and, have an improvement in psychosocial and occupational functioning.

The *continuation phase* follows the acute phase to preserve and stabilize the remission. It is the phase in which the treatment is extended for a period of time in order to prevent a return of the depression. If the depressive syndrome returns during the continuation therapy, it is considered a "relapse" of the same episode. Unfortunately, it is not possible to separate relapse from recurrence (new episode) in treated patients. Therefore, the actual length of the continuation phase cannot be validly defined empirically. In principle, recovery may be confirmed by continued absence of depressive symptoms after the cessation of medication. Recovery applies only to

Figure 2. Phases of disease and treatment.

individual episodes of the illness and does not imply that the patient will be free of recurrences thereafter (Bauer and Helmchen 2000; Moller et al. 2003).

Maintenance (prophylactic) treatment is aimed at preventing recurrence of depression and suicide as well as to enable full and lasting functional recovery (see Part 2 of these guidelines).

2. Acute-phase treatment of major depressive disorder

These guidelines become applicable at the point when the diagnosis of a major depressive episode has been made by a physician according to one of the two established classification systems – e.g., the International Classification of Diseases (ICD-10, WHO 1992) or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, APA 1994; Table II) – and when the following have been thoroughly considered: concurrent psychiatric disorders (mania, schizoaffective disorders, alcohol or substance abuse/dependence, anxiety disorders, eating disorders, personality disorders) and somatic disorders (e.g., endocrine, neurological, autoimmune, infectious disorders, carcinomas), as well as other factors (e.g., non-psychiatric medications or psychosocial stress factors) that might contribute to a depressive syndrome or interfere with treatment. It should be emphasized that the initial assessment of depression, including a thorough somatic examination, should be done by a physician.

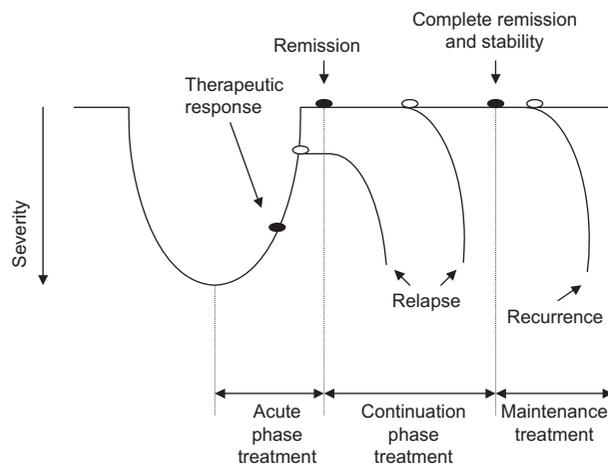The most common treatments for major depressive disorder will be reviewed below, with a focus on

somatic treatment interventions. Components of psychiatric management and general "psycho-therapeutic support" (APA 2000) should be initiated and continued throughout the entire treatment. These components include: determining the treatment plan and treatment setting; establishing and maintaining a therapeutic alliance; monitoring and reassessing psychiatric status (including the patient's risk for sui-cide); reassessing the adequacy of diagnosis; monitor-ing the patient's treatment response, side effects and general medical condition, and enhancing treatment adherence by providing education to patients and families (APA 2000). During the acute treatment phase, weekly visits (once per week, minimum) are recommended where feasible. During the continua-tion phase, the frequency of visits may vary, but a frequency of one visit every 1–2 months is recom-mended. Participation in (guided) self-help groups should be recommended if appropriate and available.

2.1 Treatment algorithms

Within this guideline, individual treatment approaches are reviewed sequentially. It should be kept in mind that these should ideally be delivered in a setting using treatment algorithms, guideline-based proce-dures, and/or collaborative-care systems, all of which have been recognized as effective methods in opti-mizing the delivery of treatment, to avoid treatment-resistant depression (Adli et al. 2003; Mann 2005; and reduce treatment costs Ricken et al. 2011; for a review see Adli et al. 2006). In the review, systematic treatment algorithms are described as to provide three types of guidance: (1) strategies (what treat-ments to use), (2) tactics (how to implement the treatments), and (3) treatment steps (in what order to implement the different treatments). These algo-rithms were developed to decrease inappropriate variance and improve the selection and implementa-tion of appropriate treatment strategies. Several algo-rithms were developed and studied within the last years, including:

- The Texas Medication Algorithm Project (TMAP; Gilbert et al. 1998; Trivedi et al. 2004).
- The Sequenced Treatment Alternatives to Relieve Depression study (STAR*D; Fava et al. 2003b; Rush et al. 2004).
- The German algorithm project (GAP; Adli et al. 2003; Bauer et al. 2009a).

Results showed treatment using systematic algo-rithms in depression therapy was superior when compared to standard treatment (see Adli et al. 2006). Whenever appropriate, results were included in the respective sections below.

2.2 Antidepressants

The development of antidepressant medications has proven to be one of the most important achieve-ments in the treatment of major depression. Since the introduction of the first tricyclic antidepressant (TCA), imipramine, in 1957, many different types of antidepressants have been introduced to the pharmacotherapeutic armamentarium. While there are currently at least 38 different antidepressants available worldwide, the availability on the markets within individual countries varies considerably (see Table III).

The "newer" antidepressants were primarily devel-oped with an aim of reducing side effects. The classes of antidepressants currently available differ little in their antidepressant efficacy, all producing treatment responses of 50–75%.

The selection of a particular antidepressant for the individual patient, therefore, depends on various factors (adapted from AHCPR 1993): patient's prior experience with medication (positive/negative response), concurrent medical conditions that may be worsened by selected antidepressants (e.g., metabolic syndrome), concomitant use of non-psychiatric medications that may lead to negative, potentially harmful drug–drug interactions (see Table VI. Possible interaction of antidepressants with comedications), a drug's short- and long-term side effects (side effects which affect quality of life are critical for patients' satisfaction and adherence), physician's experience with the medication, patients' history of adherence to medication, history of first-degree relatives responding to a medication, patient preferences, and the cost and availability of specific antidepressants.

Whether the degree of benefit attained from adequate treatment increases proportionally with the severity of depression is still a matter of controversy (Angst and Stassen 1994; Melander et al. 2008; Gibbons et al. 2012).

2.2.1 Classification and efficacy. Unfortunately, the classification of antidepressants used in clinical prac-tice does not always reflect a systematic approach. Traditionally, antidepressant medications have been grouped into the following main categories: tricyclic antidepressants (TCA), tetracyclic antidepressants (both are non-selective serotonin and norepineph-rine reuptake inhibitors), selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors (NRIs), selective serotonin and norepi-nephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOI) (including irreversible MAOIs and reversible inhibitors of monoamine

oxidase A [RIMA]), and "other" antidepressants.[2] The latter group includes substances such as tetra-cyclics, bupropion (a noradrenaline and dopamine reuptake inhibitor, NDRI), tianeptin (a 5-HT reuptake enhancer) and agomelatine (a melatonin receptor agonist and antagonist at postsynaptic 5-HT2c receptors). The categories are used in these guidelines, however, due to the unsystematic nature of this classification, antidepressants are listed in Table III in alphabetical order.

The "older" antidepressants have, in numerous placebo-controlled studies, proved effective in treating major depressive disorder. They include the tricyclics, tetracyclics and irreversible MAO inhibitors (Khan et al. 2000; Storosum et al. 2001; Fiedorowicz and Swartz 2004). It has been estimated from double-blind trials that 50–75% of patients with severe to moderate severe major depression respond to tri- and tetracyclic antidepressants compared to 25–33% treated with placebo (APA 2000). However, the magnitude of the effect is rather modest compared with placebo in milder forms of major depression, particularly in primary care studies (Paykel et al. 1988; Anderson et al. 2000).

Similarly, numerous double-blind controlled trials have demonstrated superior efficacy of the SSRI compared to placebo (AHCPR 1999; Bech et al. 2000; Khan et al. 2000; Mace and Taylor 2000). Compared to supportive care alone, SSRI plus supportive care was associated with lower HDRS scores and higher scores on quality of life and satisfaction in depressed patients in general practice (parallel group, open-label, pragmatic randomized controlled trial in general practice, THREAD, Kendrick et al. 2009).

In addition, the efficacy of SNRIs compared to placebo has been demonstrated in numerous double-blind controlled trials (Entsuah et al. 2001; Hirschfeld and Vornik 2004). For mirtazapine and agomelatine, the efficacy compared to placebo is also well documented (Bech (2001) and Hickie and Rogers (2011), respectively). The NRI reboxetine was found in a meta-analysis by Eyding et al. (2010) (that included unpublished data by the manufacturer Pfizer) not significantly more effective than placebo.

The effect size of antidepressants compared to placebo was estimated to be 0.39 (CI 0.24–0.54) (Moncrieff et al. 2004). However, Moller et al. (2012) noted, that this only provides a global estimate of the average efficacy with no insight into individual patient or patient subgroup responses. The latter could be considerably higher (Montgomery and Kasper 2007), e.g., due to decreasing the variance when looking into special subgroups of patients. Furthermore, efficacy measures do not easily display clinical relevance. Percentage of patients with response or remission is considered to be a meaningful measure of clinical relevance (Montgomery and Moller 2009). Considering response, the placebo-verum difference was estimated to be roughly between 10 and 20% (Storosum et al. 2001; Barbui et al. 2008; Melander et al. 2008; Leucht et al. 2012), corresponding to a Number Needed to Treat (NNT) of 5–7.

The "older" (irreversible) MAO inhibitors (e.g., tranylcypromine and phenelzine) are not considered first-line treatments. Although their efficacy is comparable to tricyclic antidepressants, they entail the risk of potentially fatal hypertensive crisis or serotonin syndrome (see below) in patients who eat foods containing tyramine (e.g., aged cheese, aged or cured meats, soy sauce and soy bean condiments, salted fish, and red wine; see manufacturer's warning notices) or use certain medications (APA 2000).

2.2.2 Comparative efficacy and tolerability. The numerous tricyclics do not differ among themselves in terms of efficacy, but do show different side effect profiles (Table IV) (Hotopf et al. 1997). For outpatients, meta-analyses revealed comparable overall efficacy of the irreversible MAO inhibitors (phenelzine, isocarboxazid and tranylcypromine) (Thase and Rush 1995; APA 2000). In one meta-analysis, the reversible, selective MAO-A inhibitor, moclobemide, was found to be slightly less effective but better tolerated than "older" MAOIs (Lotufo-Neto et al. 1999). Moclobemide has shown equal efficacy compared with imipramine in a placebo-controlled trial (Versiani et al. 1989). Regarding differences in efficacy and tolerability between "newer" antidepressants, Cipriani et al. found in a direct and indirect-comparison meta-analysis of 117 RCT with 25,928 patients that mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine. The NRI reboxetine was significantly less effective than all other antidepressants tested (Cipriani et al. 2009). The last finding was substantiated by the above-mentioned meta-analysis by Eyding et al. (2010) that included unpublished data by the manufacturer Pfizer.

In general, there are no clinically significant differences in efficacy and effectiveness between tricyclic antidepressants and SSRI (Anderson et al. 2000;

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[2]Note: Abbreviations used for antidepressant groups vary in the literature. For example, selective norepinephrine reuptake inhibitors are abbreviated as NRI or SNRI, selective serotonin and norepinephrine reuptake inhibitors as SNRI or SSNRI.

Table IV. Side Effect Profiles of Antidepressants.[1]

Generic Name (in alphabetical order)	Anti-cholinergic[2]	Nausea/Gastro intestinal	Sedation	Insomnia/Agitation	Sexual dysfunction	Orthostatic hypotension	Weight gain	Specific adverse effects	Lethality in overdose
Agomelatine	–	+	–	–	–	–	–	Risk of liver damage	Low
Amineptine	–	+	–	++	+	–	+	Risk of abuse (amphetamine-like effects)	Low
Amitriptyline	+++	–	+++	–	+	+++	+++	ECG changes[3]; may lower seizure threshold	High
Amoxapine	+++	+	+	++	+	+	+	hyperprolactinemia	High
Bupropion	+	+	–	+	–	–	–		Low
Citalopram	–	++	–	++	++	–	–		Low
Clomipramine	+++	+	+	+	++	++	++	ECG changes[3]; may lower seizure threshold	Moderate
Desipramine	+	–	–	++	+	++	+		High
Dibenzepine	+	–	–	–	+	+	+		Moderate
Doslepine	++	–	++	–	+	+	+		High
Dothiepin	+++	–	+++	++	+	+++	+++		High
Doxepine	+++	–	+++	++	++	+++	++		High
Duloxetine	–	++	–	–	++	–	–		Low
Escitalopram	–	++	–	+	+	–	–		Low
Fluoxetine	–	+++	–	++	+	–	–		Low
Fluvoxamine	+	+++	+	+	+	–	–		Low
Imipramine	++	–	+	++	+	++	++	ECG changes[3]; may lower seizure threshold	High
Isocarboxazid	+	+	–	++	+	++	+	Hypertensive crisis[5]; risk of serotonin syndrome[6]	High
Lofepramine	+	–	+	++	+	+	+	ECG changes[3]; may lower seizure threshold	Low
Maprotiline	++	–	++	–	–	++	++	Increased seizure risk	High
Mianserin	+	++	++	–	–	+	+	Blood dyscrasia (rare)	Low
Milnacipran	–	–	–	++	++	–	–		Low
Mirtazapine	–	–	++	–	–	+	++		Low
Moclobemide	+	+	–	++	–	–	–		Low
Nefazodone	+	+	++	–	–	+	+	Inhibitory effects on CYP3A4[4]	Low
Nortriptyline	+	–	+	+	+	+	+	ECG changes[3]; may lower seizure threshold	High
Paroxetine	+	++	–	–	++	–	+	Inhibitory effects on CYP2D6[4]	Low
Phenelzine	+	+	+	++	++	++	+	Hypertensive crisis[5]; risk of serotonin syndrome[6]	High
Protriptyline	+++	–	+	++	+	+++	+	ECG changes[3]; may lower seizure threshold	High
Reboxetine	–	+	–	++	–	++	–		Low
Sertraline	–	++	–	++	++	–	–		Low
Setipiline	+	–	++	–	–	+	+		Moderate
Tianeptine	+	+	–	+	–	–	–	ECG changes[3]; may lower seizure threshold	Low
Tranylcypromine	–	+	–	++	+	++	–	Hypertensive crisis[5]; risk of serotonin syndrome[6]	High
Trazodone	+	+	++	–	+	++	+	Priapism (rare)	Low
Trimipramine	++	–	+++	–	+	++	++	ECG changes[3]; may lower seizure threshold	High
Venlafaxine	–	++	–	++	++	–	–	Hypertension	Low
Viloxazine	–	+	–	++	–	–	–		Low

Categories of side effect strength: +++ (high/strong), ++ (moderate), + (low/mild), – (very low/none).

[1] These side effect profiles of antidepressants are not comprehensive and are for rough comparison only. Details of drugs used and potential cautions and interactions should be looked up in textbooks/reviews (e.g., Benkert and Hippius 2005; Bezchlibnyk-Butler and Jeffries 1996; Kent 2000), the primary literature or the complete prescribing information available in the package insert of the drug.

[2] These refer to symptoms commonly caused by muscarinic receptor blockade including dry mouth, sweating, blurred vision, constipation and urinary retention.

[3] Conduct delays.

[4] Only those inhibitory effects on hepatic CYP450 enzymes are shown that are clinically relevant; for details see Brøsen (1998) and Kent (2000).

[5] Increased risk with high tyramine containing food and sympathomimetic drugs.

[6] In combination with serotonergic drugs.

APA 2000; Bech et al. 2000; Geddes et al. 2001; Cipriani et al. 2005). One meta-analysis did show evidence that TCAs may be slightly more effective than SSRI in hospitalized patients and severely ill patients (Anderson et al. 2000; APA 2000; see also Danish University Antidepressant Group 1986, 1990). However, another meta-analysis of fewer RCTs using a different methodology found that the advantage of TCAs over SSRI did not reach statistical significance (Geddes et al. 2001). There was also no significant difference in efficacy found when comparing mirtazapine with TCA (meta-analysis of Watanabe et al. 2008).

Side effects vary between classes of antidepressants and to some extent between individual agents. SSRI are generally tolerated better than TCAs and show lower rates of treatment discontinuation (Simon et al. 1996; AHCPR 1999; Anderson et al. 2000; Bech et al. 2000; Peretti et al. 2000; see also the review by Vaswani et al. 2003). SSRI are safer and have higher tolerability profiles than tricyclic and tetracyclic antidepressants, causing fewer anticholinergic side effects and cardiovascular toxicities (Mace and Taylor 2000; Peretti et al. 2000; Ray et al. 2004). An agent may have a side effect profile which makes it particularly suitable for patients with specific concurrent, non-psychiatric medical conditions. For patients with coronary artery disease, for example, drugs that do not lower blood pressure or are not associated with changes in cardiac conduction (e.g., bupropion, SSRI) are preferable. Among the tricyclics, the secondary amines (e.g., desipramine, nortriptyline) have fewer side effects than do the tertiary amines (e.g., amitriptyline, imipramine).

The most frequent side effects of TCAs and tetracyclics are: anticholinergic/antimuscarinergic (dry mouth, constipation, blurred vision, urinary retention, and tachycardia), cardiovascular (α-adrenergic blockade, orthostatic hypotension, brady-arrhythmias, tachycardia), antihistaminergic (sedation, weight gain), and neurological (mild myoclonus, seizures in overdoses, delirium in elderly patients). TCAs and tetracyclics should, therefore, not be used in patients with moderate to severe cardiovascular disorders (Shores et al. 1998), narrow-angle glaucoma, prostatic hypertrophy, cognitive impairment, seizures or delirium. Where TCA are indicated because other options failed nortriptyline has a rather safe cardiac safety profile.

The most frequent side effects of SSRI are: gastrointestinal (nausea, vomiting and diarrhea), activation/restlessness (exacerbation of restlessness, agitation, sleep disturbances), sexual dysfunction (loss of erectile or ejaculatory function in men, loss of libido and anorgasmia in both genders) and neurological (exacerbation of migraine headaches and tension headaches). SSRI can alter platelet function, especially in combination with other substances influencing platelet function. Therefore, monitoring of clinical signs and bleeding time is advised. In addition SSRI have a considerable risk of SIADH (low serum sodium). Finally high doses of SSRIs have been associated with QTc prolongation (e.g., citalopram, escitalopram).

The use of SSRI is contraindicated in combination with or shortly before/after treatment with MAO inhibitors because of the risk of serotonin syndrome. The most frequent clinical features of the serotonin syndrome are changes in mental status, restlessness, myoclonus, hyperreflexia, shivering, abdominal pain, diarrhoea and tremor (Sternbach 1991; Finfgeld 2004). The serotonin syndrome is most commonly the result of the interaction between irreversible MAO inhibitors and SSRI but can also occur with other serotonergic agents (e.g., clomipramine, L-tryptophan, fenfluramine, buspirone, venlafaxine, milnacipran, nefadozone, trazodone and, in rare cases lithium).

Side effects with the SNRI venlafaxine and duloxetine are more frequent than with the SSRI escitalopram and sertraline, leading to more discontinuations of treatment, whereas milnacipran did not (Cipriani et al. 2009). Blood pressure should be monitored for possible elevation.

Mirtazapine did lead to similar rates of discontinuation of treatment as SSRI. Weight gain and sedation may be induced but nausea and sexual dysfunction occurred less frequently (Watanabe et al. 2011).

With agomelatine an increased risk of liver damage has to be considered (with up to 10-fold increase of transaminases, some cases of liver failure, hepatitis, icterus). Regular monitoring of liver enzymes is mandatory at the start of treatment and dosage increase.

Antidepressants differ with regard to the sexual side effects (Ferguson 2001; Montejo et al. 2001; Montgomery et al. 2002; Damsa et al. 2004). TCA, SSRI and venlafaxine more likely cause sexual dysfunction than duloxetine and reboxetine (Werneke et al. 2006), mirtazapine less likely than SSRI (Watanabe et al. 2011) and bupropion is less likely than fluoxetine, paroxetine, sertraline and escitalopram (Gartlehner et al. 2007). For agomelatine, the rate of sexual side effects seems not different from placebo (Dolder et al. 2008). For managing antidepressant sexual side effects see Zajecka (2001) and Worthington and Peters (2003).

Use of antidepressants in mild, moderate and severe depression

In the consulted up-to-date international guidelines (NICE 2009; CANMAT 2009; DGPPN et al. 2009;

APA 2010) and other evidence from the systematic literature search, there is substantial agreement regarding the use of antidepressants and the preferable drug class in the treatment of moderate to severe depression.

SSRI are mostly considered as a first-line option, followed by mirtazapine, SNRI and tetracyclics, bupropion, tianeptin and agomelatine. TCA are usually considered as a second-line option. Regarding MAO-Inhibitors, there is less agreement, with the reversible inhibitor moclobemide often seen as a first-line option, the other MAO-Inhibitors as second- or third-line options. They are mainly seen as an option in treatment-resistant depression (see Section 2.9).

Guidelines and physicians vary most in regards the question of when to use antidepressants in mild depression. Weighing benefits and risks of medication against proven benefits of psychotherapies efficacious in the acute treatment of moderate to severe depression (e.g., CBT, IPT), these approaches, psychoeducation alone, or even "watchful waiting" (for approximately 2 weeks, accompanied by general support) are considered appropriate. This may differ in patients with a past history of moderate or severe depression, with initial presentation of subthreshold depressive symptoms present for a long period (typically at least 2 years) or with subthreshold depressive symptoms or mild depression that persist(s) after other interventions (see DGPPN et al. 2009; NICE 2009; APA 2010; Baghai et al. 2011).

WFSBP recommendation:

For *mild* depressive episodes, psychoeducation or psychotherapies efficacious for moderate to severe depression are treatment alternatives to antidepressants.

Where medication is used (wish/preference of the patient, positive experience of the patient with response to medication treatment in the past, moderate or severe episodes in the past[1] or if initial non-pharmacological trials failed), SSRI and other "newer antidepressants" (apart from reboxetine) are first-choice medications.*

For *moderate* depressive episodes, SSRI and other "newer antidepressants" (apart from reboxetine) are first choice medications.**

For *severe* depression, TCA, SSRI and SNRI can be recommended.***

CE A, RG 1

[1]S3 Guideline DGPPN et al. (2009), *in monotherapy or in combination with psychotherapy, **in monotherapy or in combination with psychotherapy, ***and ECT or MAO-I, if appropriate.

Regarding the question whether initial therapy should consist of either mono- or combination therapy, a recent meta-analysis of five small studies published up until August 2010 concluded that the combination of SSRI with mirtazapine and SSRI with TCA is superior to SSRI alone, with no difference in drop-out rates due to adverse events (Lopes et al. 2012, limitations because of total cases included and heterogeneity of antidepressants included have to be considered). In contrast, results from the single-blind controlled CO-MED study (Combining Medications to Enhance Depression Outcomes, Rush et al. 2011) showed no superiority of combination treatment (bupropion+escitalopram or venlafaxine+mirtazapine) to monotherapy (escitalpram) and, instead, showed a higher rate of adverse events with venlafaxine+mirtazapine. Yet, in another study, combination treatment involving mirtazapine, fluoxetine, venlafaxine, and bupropion was clearly superior to fluoxetine monotherapy (Blier et al. 2010).

2.2.3 Specific clinical features influencing the treatment plan. The degree of benefit from adequate treatment appears to increase with severity of depression (Kirsch et al. 2008; Fournier et al. 2010). For mild depressive episodes, education, support, and problem solving are treatment alternatives to antidepressants. With increasing severity, antidepressants become more and more relevant. Individuals with a major depressive episode frequently present with features and symptoms in addition to those required for diagnosis according to DSM-IV (or ICD-10) criteria. There is some indication that the different subtypes of major depression respond differentially to the various classes of antidepressants.

2.2.3.1 MDD with melancholic features and hospitalization. Melancholic features include loss of pleasure in most or all activities and/or lack of mood reactivity to usually pleasurable stimuli, early morning waking, morning worsening, significant weight loss, psychomotor retardation/agitation, and a distinct quality of the depressed mood which does not resemble grief. The majority of patients who meet the DSM-IV criteria for melancholic subtype also have high levels of severity but not all patients with "severe depression" have melancholic features. Hospitalized patients also frequently present with melancholic features. According to meta-analyses, the results of which do not necessarily reflect clinical relevance, paroxetine (Tignol et al. 1992), venlafaxine (Entsuah et al. 1995) and moclobemide (Angst and Stabl 1992) are more effective than placebo in melancholic depressed patients and as effective as

TCA comparators. In the Danish DUAG studies, remission rates of hospitalized depressed patients, most of whom had melancholic features, were significantly higher in those treated with clomipramine as compared to paroxetine, citalopram, and moclobemide (Danish University Antidepressant Group 1986, 1993, 1999). There is also some evidence that amitriptyline and clomipramine, as well as venlafaxine, may be more effective than the SSRI in the treatment of patients with severe melancholic depression (Perry 1996; Anderson 2001).

2.2.3.2 Psychotic depression.
Major depressive disorder may be associated with delusions and/or hallucinations. Patients with psychotic depression may have a considerably better response rate to the combination of an antidepressant plus an antipsychotic than to treatment with either component alone (Spiker et al. 1985; Rothschild et al. 1993; Bruijn et al. 2001; Thase 2002; Rothschild 2003; Shelton 2003; Klein et al. 2004; Kunzel et al. 2009; Wijkstra et al. 2010). This is also true for venlafaxine, compared to venlafaxine plus quetiapine Wijkstra et al. (2010).

WFSBP recommendation:

> In patients with psychotic depression a combination of an antidepressant with an antipsychotic medication is recommended when treatment is initiated.
>
> CE B, RG 3

In a meta-analysis combining two studies (Spiker et al. 1985; Mulsant et al. 2001), the combination of a tricyclic antidepressant with a classical antipsychotic was more efficacious than the tricyclic alone; although the difference did not reach statistical significance (OR 1.44 [95% CI 0.86–2.41], Wijkstra et al. 2006).

Atypical antipsychotics are sometimes preferred over the classic antipsychotics due to their lower risk of extrapyramidal symptoms (Ostroff and Nelson 1999; Corya et al. 2003; Barbee et al. 2004; Masand 2004). However, the higher risk of metabolic syndrome with atypical antipsychotics should be considered.

No controlled data are available that have compared the newer with the older antipsychotics in psychotic depression. A recent meta-analysis of 519 patients, Farahani and Correll (2012) found that antidepressant-antipsychotic combined treatment was superior to both antidepressant and antipsychotic monotherapy in the acute treatment of psychotic depression. The authors warrant detailed studies testing more specific combinations and more studies testing atypical antipsychotics and newer antidepressants.

Usually, antipsychotics are administered to depressed patients at lower doses than those used in schizophrenia.

2.2.3.3 MDD with atypical features.
Atypical features are mood brightening in response to events, hypersomnia, weight gain, intense fatigue, leaden paralysis of limbs, and rejection sensitivity as a personality trait. There is substantial evidence that particularly depressed patients with atypical features benefit from the irreversible MAOIs (Quitkin et al. 1991; Nierenberg et al. 1998). In a meta-analysis, both phenelzine and tranylcypromine appeared to be more effective than imipramine in depressed outpatients with atypical features (Thase et al. 1995). There is, however, a lack of comparison studies against newer antidepressants including SSRI that are the first choice in "typical" depression.

2.2.3.4 Suicidal depression.
Suicide is a significant risk in patients with major depression. Therefore, individual suicide risk should be assessed during the first visit and reviewed regularly over the course of treatment. Inpatient treatment becomes mandatory in case of acutely increased suicidality. Factors alerting the physician of an potentially increased risk of suicide are: affective illness, poor impulse control, despair and hopelessness, age and gender (males between the ages of 20 and 30 and over age 50 years and especially very old males; and females between the ages of 40 and 60), history of previous suicide attempt (the most relevant factor), family history of suicidal behaviour, positive family history of early-onset affective disorder, substance abuse (particularly alcohol abuse), marital status (single, divorced or widowed), sudden change in socioeconomic status (loss of job, financial problems, undesired retirement), and lack of support (Blumenthal 1990; Appleby 1992; Nordstrom et al. 1995a,b; Angst et al. 1999; Bostwick and Pankratz 2000; Moller 2003). Combination of these factors may potentiate suicide risk.

There is no specific, fast acting "anti-suicidal" medication. Adding benzodiazepines to the treatment regimen (Furukawa et al. 2001) may improve short-term control over suicidal acts. Lithium has been shown to be effective in preventing suicide attempts and completed suicide when administered prophylactically (see Part 2 of these guidelines); whether it additionally has acute anti-suicidal effects is currently not known.

ECT is seen as a first-line option in all consulted guidelines for highly suicidal patients. Antidepressants

toxicity in case of overdose of either an anti-depressants or of other medications should be taken into account and, if necessary, the amount of drug(s) accessible should be limited. After starting anti-depressant treatment in suicidal patients or those younger than 25 years (because of the potential increased prevalence of suicidality in the early stages of antidepressant treatment for this group, Stone et al. 2009), patients should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically important (NICE 2009). Regarding the toxicity of anti-depressants taken in overdose, Hawton et al. (2010) did show that venlafaxine and mirtazapine were associated with a higher case fatality index when compared to SSRI and, a much lower index when compared to TCA. Among the SSRI (that have a relatively low case fatality), citalopram was the most toxic (Hawton et al. 2010).

Additional psychotherapy is recommended that initially focuses on suicidality. The short-term aim is to form an intensive contact with the patient and to provide active, prompt support and relief until the crisis subsides. A stable and reliable therapeutic relationship can be preventive against suicide per se.

WFSBP recommendation:

> If the patient has suicidal thoughts or intent, close surveillance and specialist treatment are necessary and admission to a psychiatric ward is recommended. Hospital admittance without patient consent may be necessary. Immediate and intensive care should be initiated and should include intensive pharmacotherapy and psycho-therapy addressing psychosocial factors.
>
> Clinical consensus

WFSBP recommendation:

> For severely depressed patients at risk of taking an overdose of medication, it is recommended that physicians prescribe a limited supply (e.g., weekly) of potentially lethal antidepres-sants (e.g., TCA or irreversible MAO inhibitors) and that the antidepressant chosen is one which is relatively safe in case it is taken in overdose.
>
> Clinical consensus

Epidemiological studies revealed a reduction of the frequency of suicides and increased prescriptions of antidepressants within the last decades (Sartorius et al. 2007). In contrast, there is a debate on whether certain antidepressants, or antidepressants in general, potentially increase the risk of suicidal behaviour. Clinical conditions, such as co-morbid personality disorders and inadequate treatment of bipolar depression (especially depressive mixed states), may be of importance within this context.

Some data suggest that treatment with SSRIs, and probably other antidepressant drug classes, too, may increase risk of suicidality (preferentially suicidal attempts) in some patients (Moller 2006). This risk might be prominent shortly after treatment initiation (Jick et al. 2004). Simon et al. (2006), however, showed that the risk of suicide is highest in the month before starting an antidepressant, rapidly declining in the first week of treatment, continuing to drop to even lower, stable rates with treatment (data from computerized health plan records of 65,000 patients with depression). Khan et al. com-pared the incidence of suicide and suicide attempts with several of the "newer" antidepressants and did not find statistically significant differences to placebo (Khan et al. 2000). In a recent very comprehensive meta-analysis of trial data submitted to the FDA, Stone et al. (2009) confirmed this finding, with an odds ratio (OR) of 1.12 (95% CI 0.79–1.58) for suicide-related behaviour with antidepressant drug treatment compared to placebo, meaning no signifi-cant difference.

However, the initial concerns mentioned above led to official warnings (e.g., by the US Food and Drug Administration: FDA 2005), especially for child and adolescent psychiatry. The efficacy for most antide-pressants has not been demonstrated in this group and a meta-analysis showed an increase in suicidal thoughts and attempts (but not completed suicide) in children and adolescents (FDA 2004).

For a comprehensive discussion on the topic, see the Position Statement of the EPA on the value of antidepressants in the treatment of unipolar depres-sion (Moller et al. 2012). See also the up-to-date EPA guidance on suicidality treatment and preven-tion (Moller et al. 2008; Seemuller et al. 2009; Wasserman et al. 2012).

WFSBP recommendation:

> In medical decision making, the potential risks should be carefully balanced with the benefits of antidepressant treatment. Consideration of the individual past history including risk factors for suicidal behaviour and close observation of the patient (e.g., every week during the first weeks of treatment) are recommended when starting antidepressant treatment.
>
> Clinical consensus

For information on treatment recommendations for *MDD with Psychotic Features (Delusional Depression)*,

see Section 2.2.3.2; for *MDD with Seasonal Pattern,* see Section 2.6 (Light therapy); and for *MDD with Anxiety Features* ("Anxious" Depression), see Section 4.1.1.

2.2.4 Evaluating the efficacy of the initial treatment. Efficacy of the initial treatment can be evaluated by performing a thorough assessment of the patient's response to the antidepressant within a defined time period. In this regard, using observer-ratings scales (e.g., Hamilton Rating Scale for Depression, HRSD; Hamilton 1960, six-item version Bech et al. 1981), the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg 1979; Rush and Kupfer 2001), the Bech–Rafaelsen Melancholia Scale (BRMS/MES; Bech and Rafaelsen 1980) is recommended and may be complemented by patient self-rating scales (e.g., Beck Depression Inventory, BDI; Beck et al. 1961), the nine-item module of the Patient Health Questionnaire (PHQ-9; Spitzer et al. 1999), the Major Depression Inventory (MDI; Bech et al. 2001; Olson et al. 2003).

Recommended threshold criteria for treatment response are:

- Non-response: ≤ 25% decrease in symptom severity compared to baseline.
- Partial response: 26–49% decrease in symptom severity compared to baseline.
- Response: ≥ 50% decrease in symptom severity compared to baseline.
- Response with residual symptoms: response with partial remission.
- Remission: no symptoms or very few symptoms of minor severity are still present, defined by absolute scale score (for example a HRSD score of ≤ 7) and improvement in psychosocial and occupational functioning.

During the past five decades, a principle belief about antidepressant pharmacotherapy was that antidepressant response usually appears with a delay of several weeks. This view mainly rests on two sources: firstly, controlled clinical trials aiming to provide evidence for an antidepressants' efficacy usually compared the active compound with placebo. When comparing mean scores of rating scales as measures for depressive symptomatology, a significant difference between active treatment and placebo was usually detected from week 2–4 and onwards. This time lag to statistical separation between drug and placebo has long been misinterpreted as a delayed onset of action of antidepressants, not taking into account that also placebo causes an often substantial initial improvement of depression. Secondly, pattern analysis (Quitkin et al.

1984, 1987) has suggested that persistent or "true" drug response occurs mainly in the later course of treatment, i.e. weeks 3–4, while response occurring in the first 2 weeks was assumed to be unstable and due to placebo effects.

Challenging the idea of a delayed onset of antidepressant' action, there is a substantial body of evidence from numerous retrospective as well as ex post analyses of prospective studies involving more than 33,000 patients and treated with virtually all groups of antidepressants strongly suggesting that a true drug response can be observed within the first 14 days of treatment (Nierenberg et al. 2000; Szegedi et al. 2003; Katz et al. 2004; Posternak and Zimmerman 2005; Papakostas et al. 2006; Taylor et al. 2006; Stassen et al. 2007; Henkel et al. 2009; Hennings et al. 2009; Szegedi et al. 2009; Tadic et al. 2010b; Uher et al. 2010). Moreover, improvement of depressive symptoms during the early course of treatment has been identified as being highly predictive of a positive final treatment outcome. Multiple studies of Stassen and colleagues analysed individual time courses of response in depressed patients treated with various antidepressants (see Stassen et al. 2007). A model-finding study with repeated HAMD-17 assessments during a 1-week placebo run-in showed that the observed fluctuations did not exceed 15% of baseline score. Subsequently, onset of improvement (which models onset of action) has been defined as a 20% baseline score reduction. This threshold is in line with clinical practice in which a four-point HAMD-17 reduction (= 20% for a HAMD17 score of 20) is regarded as clinically relevant. Their analyses concordantly revealed that patients with such an improvement during the first 2 weeks of antidepressant treatment (= early improvement) also showed substantially greater response rates at study endpoint. A meta-analysis of 2,848 patients with MDD confirmed previous analyses showing that early improvers were far more likely to become responders than patients without early improvement (pooled OR = 9.25, 95%–CI = 7.79–10.98). In a separate analysis, Szegedi et al. (2003) examined early improvement in a randomized controlled trial comparing mirtazapine and paroxetine in MDD patients. Improvement (HAMD-17 score reduction ≥ 20%) occurred in a majority of patients within 2 weeks of treatment, and this improvement was a highly sensitive predictor of later stable response (HAMD-17 score reduction ≥ 50% at week 4 and onward) and stable remission (HAMD-17 score ≤ 7 at week 4 and onward) for both drugs. Less than 10% of patients who had not improved after 2 weeks of treatment became stable responders or remitters over the course of the 6-week study. Szegedi et al. (2009) and colleagues recently extended their analysis to 41

clinical trials with 6,562 MDD patients treated with either mirtazapine, serotonine reuptake inhibitors, tricyclics, venlafaxine or placebo. Again, early improvement predicted stable response and stable remission with high sensitivity (>80 and 87%, respectively). Only 11 and 4.1%, respectively, of patients, who did not improve within the first 2 weeks, became stable responders or stable remitters. Recently, these results which were obtained from secondary analyses of RCTs, have been confirmed in large cohorts of naturalistically treated patients (Henkel et al. 2009; Hennings et al. 2009) as well as in patients suffering from a mild MDE or minor depression (Tadic et al. 2010b), thereby adding additional layers of evidence. However, the negative predictive value (NPV, the proportion of non-improvers not going on to achieve response/remission at the last evaluation), which should be at about 80% or more, was lower in longer, open studies with probably more severe patients included compared to RCTs with only 6 weeks follow-up that required response at 4 weeks. Therefore, the NICE guideline suggests that a reasonable time to consider a change of treatment would be at 3–4 weeks with an average assessment period of 8 weeks and an NPV based on less than 20% improvement predicting lack of response at 8 weeks. (NICE 2009).

The finding of early improvement being highly predictive for later outcome resulted in the idea that an effective antidepressant treatment triggers and maintains biological mechanisms necessary for recovery from the disorder (Stassen et al. 2007). It has been suggested that affectively ill patients possess a biological, "resilience"-like component that controls recovery from depression to a major extent. Once triggered, recovery seems to follow a uniform course – independent of pharmacological differences between the (antidepressant) triggers. Consequently, the vast majority of patients showing a favorable later outcome experience the respective onset within the first 2 weeks of treatment. Conversely, non-improvement after 2 weeks of treatment seems to indicate that a selected antidepressant did not trigger the resilience-like component and has little chances to do so. Based on these findings from retrospective analyses, leading experts in this field have repeatedly recommended stringent symptom evaluation during the early course of treatment for clinical decision making.

However, for a clear-cut recommendation of treatment optimization in case of insufficient early improvement, evidence should be provided by high-quality and well-controlled prospective trials. In a randomized open-label trial, Nakajima et al. (2011) prospectively compared 8-week outcomes between switching and maintaining an antidepressant in early non-improvers. When subjects failed to show an early improvement (MADRS decrease $<20\%$ at week 2) to the initial treatment with sertraline 50 mg/day, they were randomly assigned to two groups: either continuing sertraline at 50–100 mg/day or switching to paroxetine at 20–40 mg/day. Of 132 subjects, 41 showed early non-improvement (31%). The switching group ($n = 20$) showed significantly higher rates of response and remission as compared to the continuation group ($n = 21$) (75 vs. 19% and 60 vs. 14%, respectively). These, yet preliminary, findings may suggest that patients with MDD who fail to show early improvement to an initial antidepressant after 2 weeks of treatment benefit from an immediate switching to another antidepressant as compared to its continuation, but placebo effects cannot be excluded. Further prospective studies examining early medication change strategies against strategies based on the traditional view of a delayed onset of action, e.g., the ongoing large German EMC Trial (Tadic et al. 2010a) are necessary for a firm recommendation on treatment changes already after 2 weeks.

As long as more consolidate evidence is missing, *discontinuation of treatment* with an antidepressant should be decided by the physician and the patient in collaboration. Changing the treatment strategy too often and to early may lead to false conclusions, e.g., that the medication is ineffective, and discourage the patient. In contrast, persistence over an extended period without any response may lead to unnecessary prolongation of the patients' suffering and duration of the episode.

2.2.5 Diagnostic reassessment and optimizing antidepressant medication. Before considering a switch in the treatment strategy, the first step should be a reappraisal of the diagnosis and adherence to the current treatment regimen. It may be important to take pharmacokinetic factors that affect plasma levels of antidepressants also into consideration. If available, plasma levels of tricyclic and some, but not all, "newer" antidepressants can be helpful in evaluating the adequacy of the dosage and the need for dose adjustment (see below and Table III) (Hiemke et al. 2011). A review of the findings from physical examinations and laboratory results can avoid overlooking coexisting general medical conditions, poorly controlled pain, non-psychiatric medications or hidden substance abuse that may underlie or be associated with the depressive episode. Persistent psychosocial stressors should also be considered as a reason for non-response to treatment. Reevaluation of the adequacy of the medication dose is also advised. Often

an optimization of the treatment can be achieved by increasing the dose of the antidepressant. This strategy is particularly useful for patients receiving TCAs or venlafaxine, but less evident in SSRI-treated patients (Baker et al. 2003; Adli et al. 2005). Licht and Qvitzau even found a lower response rate with a substantial dose increase of sertraline than with staying at the same (moderate) dose for another 5 weeks (Licht and Qvitzau 2002). In a recent randomized SPECT study Ruhe et al. (2009) demonstrated that the standard dose of 20 mg/day of paroxetine leads to a nearly complete inhibition of serotonin re-uptake (about 80% occupancy of serotonin transportes). In the control group, a mean dosage of 46.7 mg/day did not lead to a higher occupancy of serotonin transporter. This might explain why dose escalation of SSRIs has not been proven effective. For a review see Adli et al. (2005).

WFSBP recommendation:

> In case of inadequate response to antidepressant treatment, assessing adherence to the current treatment regimen is recommended as a first step.
>
> Clinical consensus

2.2.6 Therapeutic drug monitoring. Therapeutic drug monitoring (TDM) involves measuring the plasma concentration of a drug to ascertain whether concentrations are above, below or within an optimal therapeutic range. Other indications for TDM are to determine absorption of and adherence with medication ingestion, and to determine if a patient is a "rapid" or "slow" metabolizer (see below). TDM is an important tool in assessing clinical response (in particular in some TCA; for ranges see Table III; Perry et al. 1994; Hiemke et al. 2011), evaluating toxic effects and monitoring for unwanted drug–drug interactions. Specifically, TDM may identify the subgroup of patients who are at risk for developing excessive plasma TCA levels that may potentially result in central nervous system and cardiovascular toxicity (Preskorn and Fast 1991; Perry et al. 1994; Brosen 1996).

Unlike with some tricyclic antidepressants, there is in general no clear relationship between clinical efficacy and plasma concentration of SSRI, nor any threshold that defines toxic concentrations (see also Adli et al. 2005). Recent data for citalopram did show that depressed inpatients had a significantly greater decrease in depression ratings with a plasma levels of at least 50 ng/mL compared to lower levels. Reasons discussed by the authors were compliance problems and rapid metabolism of the drug, leading

them to suggest TDM in the early phase of treatment (Ostad et al. 2011). In depressed elderly patients, TDM of SSRI may influence clinical dosing strategies and thus reduce drug costs (Lundmark et al. 2000). Moreover, it should be considered that depression is a significant risk factor for non-adherence with medical treatment (DiMatteo et al. 2000). TDM may therefore be useful in situations where poor adherence is suspected and when therapeutic failure or toxic events are experienced at clinically used dosages (Rasmussen and Brosen 2000).

2.2.7 Pharmacokinetics and pharmacogenetics of antidepressants. Plasma concentrations of antidepressants vary considerably among patients treated with similar dosages. Most antidepressants and antipsychotics are metabolized by the polymorphic cytochrome P450 system (CYP450), a large group of related isoenzymes located primarily in the liver. Of more than 50 human isoenzymes identified to date, cytochrome P4501A2 (CYP1A2), CYP2C, CYP2C19, CYP2D6, and CYP3A4 are most important for catalyzing the biotransformation of psychotropic drugs. The CYP2D6 isoenzyme is the primary enzyme that catalyzes more than 30 clinically used drugs, including all of the tricyclic antidepressants, several neuroleptics, opiates, beta-adrenergic blockers, antiarrhythmics and most SSRI (Brosen 1998).

"Slow" ("poor") metabolizers are individuals who possess no or limited activity of a CYP450 isoenzyme as a result of a genetic polymorphism (genetic polymorphism is defined as a CYP450 gene with a variant allele being present in at least 1% of the population). "Rapid" ("fast" or "extensive") metabolizers are individuals who have one or more CYP450 isoenzyme that metabolizes at an accelerated rate, also as a result of genetic polymorphism. About 7% of Caucasians are "slow" metabolizers, and such patients might develop adverse drug reactions when treated with recommended doses of, for example, TCAs. In contrast, "ultrarapid" metabolizers with multiple CYP2D6 genes might require high doses of such drugs for optimal therapy (Bertilsson et al. 1997; Kirchheiner et al. 2004). However, only 10–30% of the ultrarapid metabolizer phenotypes may be diagnosed having duplicated alleles (Lovlie et al. 2001). Further research is needed to characterize the majority of ultrarapid metabolizers. Of importance, the mean activity level of CYP2D6 is lower in Asian populations than in Caucasian populations because of a common mutation that causes decreased enzyme activity (CYP2D6*10).

WFSBP recommendation:

> In possibly non-adherent patients (e.g., low drug plasma levels despite high doses of the antidepressant), a combination of TDM and genotyping may be informative. Such analyses can aid in identifying those individuals who are slow or rapid metabolizers of certain antidepressants.[1]
>
> Clinical Consensus

[1]See Bertilsson et al. (1997), Tanaka and Hisawa (1999), Steimer et al. (2001), Kirchheiner et al. (2004).

Pharmacokinetic drug–drug interactions may occur when drugs are metabolized by the same CYP450 isoenzyme. One type of interaction occurs when a CYP450 isoenzyme is stimulated by certain agents that affect the metabolism of drugs metabolized by the same enzyme (induction). This interaction results in decreased plasma levels and generally reduced clinical effect. Another type of interaction occurs when two agents metabolized by the same enzyme compete for the process of elimination (inhibition). This interaction results in increased plasma levels and potentially toxic effects (for information on potential drug–drug interactions between frequently prescribed antidepressants and other medications, see Michalets 1998; Kent 2000; Kennedy et al. 2001). In addition to induction and inhibition, drug metabolism in the liver is affected by genetic polymorphisms, age, nutrition, hepatic disease, and endogenous chemicals (Michalets 1998). Most importantly, the detection of drug–drug interactions may be important in treating patients with comorbid illnesses taking non-psychotropic medications (Kent 2000).

SSRI vary widely in their qualitative and quantitative interaction with CYP450 isoenzymes. CYP2D6 is inhibited by SSRI (in order of decreasing potency: paroxetine, norfluoxetine and fluoxetine) (Hiemke and Hartter 2000). The CYP2D6 inhibitory activity of sertraline, citalopram and fluvoxamine are of negligible clinical relevance (Baumann 1996). Due to its potent CYP2D6 inhibiting properties, comedication with fluoxetine or paroxetine can lead to an increase of tricyclic antidepressants in plasma, as shown with amitriptyline and trimipramine (Baumann 1996; Kent 2000). Fluvoxamine is a strong inhibitor of CYP1A2 and CYP2C19 which contribute to the metabolism of most tertiary amines (Chiba and Kobayashi 2000). Norfluoxetine, the major metabolite of fluoxetine, and nefazodone are inhibitors of CYP3A4, another enzyme involved in phase I reactions of multiple psychotropic drugs.

WFSBP recommendation:

> If antidepressants that are inhibitors of CYP isoenzymes are combined with other drugs metabolized by the same CYP isoenzymes, plasma drug concentrations should be monitored during the course of treatment.
>
> Clinical consensus

Although "newer" antidepressants (venlafaxine, mirtazapine, duloxetine, agomelatine or reboxetine) are also metabolized through the CYP450 systems, they are associated with low drug–drug interactions compared to SSRI (Kent 2000).

2.2.8 Theoretical treatment options for the partial- and non-responding patient to initial treatment. Regardless of the initial choice of antidepressant, at least 30% of depressed patients will not respond sufficiently to treatment (Thase and Rush 1995; Tranter et al. 2002; Nelson 2003). Various alternative treatment strategies have been proposed for these non- or partially responsive depressions (Amsterdam 1991; Nolen et al. 1994; Marangell 2001; Shelton 2003; Pridmore and Turnier-Shea 2004). The major types of theoretical strategies employed after reviewing correctness of diagnosis and sufficiency of drug dosing and adherence, are:

(1) Increasing (maximizing) the dose of the initial antidepressant.
(2) Switching to another antidepressant from a different pharmacological class (e.g., from a SSRI to a TCA or a dual-acting AD).
(3) Switching to another antidepressant within the same pharmacological class (e.g., from a SSRI to another SSRI).
(4) Combining two antidepressants from different classes (e.g., an SSRI or a dual-acting AD with e.g., mirtazapine).
(5) Augmenting the antidepressant with other agents (e.g., lithium, thyroid hormone or atypical antipsychotics) to enhance antidepressant efficacy.
(6) Combining the antidepressant with a psychotherapeutic intervention.
(7) Combining the antidepressant with non-pharmacological biological therapies (e.g., wake therapy, light therapy, ECT).

These strategies have been examined in a variety of agents and combinations; however, most studies have not been subjected to rigorous scientific methods or have included small study groups. Furthermore, most used combination treatments were derived from theoretical viewpoints and are not

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supported by data from double-blind controlled studies. Thus, empirical data concerning the choice of the appropriate strategy are limited. This is especially true for switching to an antidepressant drug with a different neurochemical mechanism of action and for combining multiple antidepressants, two alternative strategies often applied for second-line treatment in clinical practice.

In the analyses of data from STAR*D patients, it was shown that the percentage with remission could be increased from 27% with initial treatment to a cumulative ratio of 67% considering all four consecutive steps of treatment sequences, but also that the probability of achieving remission was higher during the first two steps (20–30%) than during the last two (10–20%, Gaynes et al. 2009).

Currently, no clear consensus exists on which strategy should be favoured for the non-responding patient (Crismon et al. 1999; Lam et al. 2004). Some authors have argued in favour of augmentation strategies, e.g., lithium, because they have been repeatedly investigated in placebo-controlled trials. A recent retrospective analysis of data from STAR*D patients who did not respond to the initial treatment strategy, however, did not indicate whether to prefer augmentation or switching as the next treatment step (Sequenced treatment alternatives to relieve depression, Gaynes et al. 2012). In a recent narrative review, Connolly and Thase (2011) did conclude that augmentation with aripiprazole or quetiapine or a switch to another first-line antidepressant should be tried first and that augmentation with lithium or T3 may improve the efficacy of the modern antidepressants but high-quality evidence is sparse and more trials should be undertaken to evaluate this. They state that antidepressant combinations and the use of traditional stimulants are understudied. The use of pindolol and buspirone for augmentation was not recommended by the authors.

In the following, strategies 1 to 5 are reviewed in detail.

2.2.8.1 Strategy 1: increasing (maximizing) the dose the initial antidepressant.

A common strategy in treatment-resistant depression is dose escalation of the antidepressant. However, the available evidence for this approach is, at best, incomplete Adli et al. (2005). For tri- und tetracyclic antidepressants, positive evidence from dose finding studies as well as from therapeutic drug monitoring exist for a dose–response relationship, which may differ according to the antidepressant tested (linear, sigmoidal, u-shape). The same holds true for venlafaxine, which seems to be more efficient at higher doses (Thase et al. 2006). Regarding SSRI, no such evidence exists. In fact, the available data suggest that the minimal effective dosage corresponds to a more than 80% occupancy of the serotonin transporter and that this percentage cannot be further increased by dose escalation. Regarding the irreversible MAO-inhibitor tranylcypromine, small studies indicate increased efficacy at higher doses (Amsterdam and Berwish 1989; Adli et al. 2008). This may be due to an additional amphetaminergic effect of tranylcypromine at higher doses which is due to the structural similarity on a molecular level between tranylcypromine and amphetamines.

2.2.8.2 Strategy 2: switching to another antidepressant from a different class.

The potential advantage of switching to another antidepressant class is that it minimizes polypharmacy, which helps prevent toxicity and negative drug–drug interactions, may lead to fewer or less severe side effects and can, therefore, improve patient adherence (Reynaert-Dupuis et al. 2002; Thase et al. 2002; Fava et al. 2003a).

Disadvantages in such a switch are a potential loss of partial efficacy by switching from initial antidepressant and the relatively long period until the second agent can develop its full antidepressive activity (delayed onset compared to augmentation or combination).

However, switching to another antidepressant (intra- or inter-class) may not be superior to continuing the initial antidepressant (Bschor and Baethge 2010), consider that data reviewed are limited to switch to TCA and SSRI. In a recent large open randomized trial Souery et al. (2011) compared switch from citalopram to desipramine or vice versa with non-switching. Remission rates were lower in the switch groups. However no randomized controlled trials are available which examined the efficacy of switching to antidepressants considered to me among the most potent, such as escitalopram, venlafaxine (Cipriani et al. 2009) or tranylcypromine (Frieling and Bleich 2006).

WFSBP recommendation:

> Switching from an SSRI to venlafaxine or tranylcypromine appears legitimate.
>
> CE C, RG 4
>
> With longer use of most antidepressants, stepdown discontinuation within a period of 1–4 weeks is recommended rather than abrupt discontinuation, as this may cause discontinuation symptoms. However, transition to the new antidepressant can be performed in an overlapping fashion in most cases. However, switching to or from an irreversible MAO inhibitor should be performed with caution and with a 2-week washout period between the two drugs (5 weeks when switching from fluoxetine).
>
> Clinical consensus

2.2.8.3 Strategy 3: switching to another anti-depressant from the same class. Antidepressants from the same class do not necessarily have the same pharmacological profile or the same chemical configuration. Thus, antidepressants from the same class may in fact have different effects and side effects in the same patient. This has especially been demonstrated in a series of open-label studies showing that patients not responsive to one SSRI have a 40–70% chance of responding to a second SSRI (Thase and Rush 1997). Another study has shown response rates from 50 to 60% when switching to another SSRI (Howland and Thase 1999). However it has to be mentioned that those trials were not properly controlled – and thus the results have to be interpreted with great caution. Switching from one TCA to another has not been well studied and results to date were not promising (response rates between 9 and 27%) (Nelson 1998).

2.2.8.4 Strategy 4: combining two anti-depressants from different classes. Adding a second antidepressant to the ongoing treatment with an antidepressant may produce a different response than either medication alone. Rational antidepressant combinations take advantage of complementary mechanisms of action to confer synergistic benefits. Reasons in support of such combination treatment include avoidance of loss of partial response with initial monotherapy. Disadvantages of this strategy are the increased risk of drug–drug interactions, potentiation of side effects and drug costs.

Although often applied in clinical practice, few controlled data in support of the utility and efficacy of this strategy exist (DeBattista et al. 2003). The addition of a TCA to an SSRI or vice versa, and also many other different combinations of antidepressants, have been tried with varying success (Nelson 1998). With the availability of even newer antidepressants, this combination is used less frequently nowadays. Furthermore, adding an SSRI to a TCA can also cause an increased blood level and delayed elimination of the tricyclic antidepressant via CYP2D6 interaction. At least nine randomized, double-blind, controlled studies showed that the combination of a reuptake inhibitor (e.g., SSRI) with an inhibitor of presynaptic autoreceptors is more efficacious than monotherapy with one of the antidepressants (e.g., Ferreri et al. 2001), only one study did not support this strategy (Licht and Quitzau 2002). Augmentation of various SSRI with mirtazapine showed promising results in open-label studies (Carpenter et al. 1999). Also the combination of the irreversible MAO inhibitor isocarboxazid with mianserin was shown to be safe (Riise and Holm 1984).

Combining irreversible MAO inhibitors with SSRI and other antidepressants which act on the serotonergic system (e.g., clomipramine, venlafaxine) should be avoided due to potentially fatal interactions (serotonin syndrome). Similarly, combinations of an SSRI with L-tryptophan should be avoided. See systematic review on combination from Dodd et al. (2005).

In the STAR*D trial, the addition of the second-generation antidepressant bupropion or the anxiolytic buspirone to the SSRI citalopram in patients that did not respond sufficiently to citalopram alone resulted in remission rates of about 30% in each group (Trivedi et al. 2006; for design issues of this multisite, prospective, sequentially randomized trial in psychiatric depressed outpatients see Rush et al. 2004).

The combination of venlafaxine with mirtazapine did result in more risk for worsening unwanted effects compared to escitalopram monotherapy (Rush et al. 2011).

WFSBP recommendation:

> Combination of an SSRI with an inhibitor of presynaptic autoreceptors (e.g., mirtazapine) is an evidence-based choice in cases where monotherapy failed. The combination of venlafaxine with mirtazapine may be accompanied by worsening side effects.
>
> CE A, RG 2

2.2.8.5 Strategy 5: augmentation of anti-depressants. This type of augmentation therapy involves adding a second drug other than an antidepressant to the treatment regimen when no response or only partial response has been achieved, with the goal of enhancing treatment. One advantage of augmentation is that it eliminates the period of transition between one antidepressant to another and builds on the partial response. Consequently, when they work, augmentation strategies can have a rapid effect. Secondly, augmentation is of benefit for patients who have had some response and may be reluctant to risk losing that improvement.

2.2.8.5.1 Lithium. Lithium has been found to augment the therapeutic effects of a broad spectrum of antidepressants including TCAs (Joffe et al. 1993; Katona et al. 1995) and SSRI (Katona et al. 1995; Baumann 1996; Zullino and Baumann 2001). A meta-analysis including 10 prospective studies provided firm evidence that lithium augmentation is superior to placebo in unipolar major depression, with response rates on average of 41.2% in the lithium group and 14.4% in the placebo group (Crossley and Bauer 2007).

WFSBP recommendation:

> Adding lithium to ongoing antidepressant treatment is recommended in case monotherapy failed.
>
> CE A, RG 2
>
> Lithium augmentation should be administered for 2–4 weeks in order to allow assessment of the patient's response. The recommended lithium serum target levels are 0.6 to 0.8 mmol/L.[1] In case of response, lithium augmentation should be continued for at least 12 months.[2,3]
>
> CE A, RG 2

[1]Bschor et al. (2003), [2]Bauer et al. (2000), [3]Bschor et al. (2002).

2.2.8.5.2 Thyroid hormones. Studies assessing the effects of thyroid hormones in treatment-resistant depression have largely focused on T_3 as the augmenting thyroid hormone. Numerous case series and at least 13 prospective trials (nine open and four controlled double-blind studies) have evaluated the use of T_3. Most studies administered 25 to 37.5 πg/day T_3 to potentiate the response to TCAs in nonresponders (Joffe et al. 1993; Altshuler et al. 2001; Bauer and Whybrow 2001). However, not all controlled double-blind studies yielded significant results in favor of T_3. A subsequent meta-analysis did not find consistent results in favour of T3 augmentation (Aronson et al. 1996). A small number of open studies have reported response rates of about 50% for treatment-resistant depressed patients using higher, supraphysiological doses of L-thyroxine (T_4) (Bauer et al. 1998, 2002a). See Lojko and Rybakowski (2007) for physiological doses of T_4.

Results from the STAR*D study, where randomized augmentation with T3 or lithium was studied (in patients that did not respond sufficiently or were intolerant to monotherapy with citalopram and to one switch or augmentation strategy not including T3 or lithium) showed no significant difference in effect but significantly less unwanted effects (and drop-outs because of this) with T3 (Nierenberg et al. 2006).

> The augmentation of antidepressants with thyroid hormones appears legitimate in cases where monotherapy failed.
>
> Thyroid hormones should be administered with caution because of potential unwanted effects.
>
> CE B, RG 3

There is some evidence regarding combination of SSRI with T3 to enhance the initial antidepressant effect in patients with MDD (without prior insufficient response to other treatments) (Cooper-Kazaz et al. 2007). This needs substantiation.

2.2.8.5.3 Atypical antipsychotics. Another strategy is to combine antidepressants with an atypical antipsychotic, a strategy formerly only used in psychotic depression.

To date, several double-blind controlled trials are available for augmentation with aripiprazole, olanzapine, quetiapine and risperidone. A Cochrane review and meta-analysis (Komossa et al. 2010) reviewed augmentation with aripiprazole, olanzapine, quetiapine and risperidone. Augmentation with aripiprazole was found to be significantly more beneficial compared to antidepressant alone but caused more unwanted effects (weight gain and EPMS) (studies included: Berman et al. 2007, 2009; Marcus et al. 2008). The results for augmentation with olanzapine were more ambiguous and accompanied by more side effects as weight gain and prolactin increase (studies included: Shelton et al. 2001, 2005; Andersen et al. 2005; Corya et al. 2006; Berman et al. 2007; Doree et al. 2007; Mahmoud et al. 2007; McIntyre et al. 2007; Thase et al. 2007; Garakani et al. 2008; Keitner et al. 2009; Nelson and Papakostas 2009). Quetiapine augmentation was significantly more effective compared to antidepressant monotherapy but more weight gain and sedation was found in this meta-analysis (studies included: McIntyre et al. 2007; Bauer et al. 2009b; El-Khalili et al. 2010). Risperidone augmentation was significantly more effective compared to antidepressant alone but benefit was not sustained during continuation phase therapy. In addition it was accompanied by more weight gain and prolactin change from baseline (studies included: Rapaport et al. 2006; Mahmoud et al. 2007; Reeves et al. 2008; Keitner et al. 2009).

A pooled analysis of two of the three aformentioned double-blind RCT (Bauer et al. 2009b; El-Khalili et al. 2010) supported the evidence for efficacy of quetiapine augmentation (Bauer et al. 2010). A recent double-blind RCT of augmentation with low-dose aripiprazole (2 mg/day) did find good tolerability but only marginal (and nonsignificant) effects (5.6% difference in response rate and 1.5 points difference in the MADRS) (Fava et al. 2012).

WFSBP recommendation:

> The augmentation of antidepressants with que-
> tiapine or aripiprazole represents an alternative
> to lithium augmentation and is recommended in
> case monotherapy failed. Potential unwanted
> effects include sedation (quetiapine), weight gain
> (quetiapine, and to a lesser extent aripiprazole)
> and akathisia (aripiprazole).
>
> CE A, RG 2

According to the prescribing information, the rec-
ommended starting dose of aripiprazole as augmen-
tation treatment for patients already taking an
antidepressant is 2–5 mg/day. Dose adjustments of
up to 5 mg/day should occur gradually, dependent
on response, at intervals of no less than 1 week, with
the maximum final dose being 15 mg/day.

According to the prescribing information, extend-
ed-release quetiapine should be started at 50 mg
once daily in the evening. On day 3, the dose can be
increased to 150 mg once daily in the evening. Depen-
dent on response, the dose can be further increased
to 300 mg/day. Doses higher than 300 mg/day have
not been studied in this indication.

*2.2.8.5.4 Other pharmacological augmentation
strategies.* Combination of an SSRI and pindolol
(a 5-HT_{1A}/beta-adrenoceptor antagonist) markedly
accelerated the speed of the antidepressant response
in previously untreated patients (Artigas et al.
1996; Portella et al. 2011). To a lesser extent, this
strategy has also been studied as an augmentation
strategy in patients with treatment-resistant depres-
sion, but results have been contradictory (Maes et al.
1996; Perez et al. 1998). In a recent review, it was
stated that despite the ability to accelerate the
response no high-quality evidence is available to
suggest that it could improve the outcome in
patients with inadequate response (Connolly and
Thase 2011).

Buspirone is a partial agonist at the 5-HT_{1A} recep-
tor. In the STAR*D trial, as mentioned above,
bupropion or buspirone were added to the SSRI cit-
alopram in patients that did not respond sufficiently
to citalopram alone. Remission rates of about 30%
were found in both groups Trivedi et al. (2006). In
a secondary analysis defining the ITT sample as
those with at least one post-baseline value (as
opposed to Trivedi et al., where only a baseline value
was necessary) buspirone was statistically less effec-
tive compared to bupropion. This, however, was
based on a difference in the depression rating scales
of one to two points (Bech et al. 2012).

As mentioned above in a recent narrative review
Connolly and Thase (2011) did not recommend the
use of pindolol and buspirone for augmentation
(Landen et al. 1998; Appelberg et al. 2001).

See Figure 3 for a flow chart on therapeutic options
in partial and non-responders to initial treatment
with an antidepressant.

2.3 Herbal remedies

For patients who are reluctant to take traditional
antidepressants, herbal remedies provide an alter-
native. There is evidence from a substantial num-
ber of controlled trials that suggests that extracts
from the plant *Hypericum perforatum* (popularly
called St. John's Wort) are more effective than pla-
cebo for the short-term treatment of mild to mod-
erate depressive disorders (Cochrane Review:
Linde et al. 2005, update 2008, Linde et al. 2008).
Compared to tricyclic antidepressants and SSRI,
there seems to be no significant difference in treat-
ment response (Linde et al. 2005, update 2008,
Linde et al. 2008). However, a placebo-controlled
multi-centre trial found no benefits of St. John's
Wort compared to placebo treatment of patients
with moderate to severe major depression (Shelton
et al. 2001a). Thus, St. John's Wort cannot be
recommended for the treatment of severe depres-
sion based upon the available data (Werneke
et al. 2004).

The standard dose of hypericum (St. John's Wort)
is 600–900 mg/day. Adverse side effects appear to
occur less frequently with St. John's Wort compared
to tricyclic antidepressants (Kim et al. 1999). As
yet, little information is available on the herb's
medium- to long-term efficacy and side effects
(AHCPR 1999; Linde and Mulrow 2001). Health
care providers should keep in mind that there is
evidence that hypericum can interact with a num-
ber of prescription drugs (for example, it can
decrease blood levels of TCAs and antiretroviral
medications used in the treatment of HIV infection,
Izzo 2004). In addition, there have been concerns
about the purity and variation in strength of the
herbal remedies.

> Hypericum (St. John's Wort) can be an option in
> patients with mild depression who prefer "alter-
> native medicine" – but intensive education about
> potential side effects and interactions has to be
> provided and potential drug interactions have to
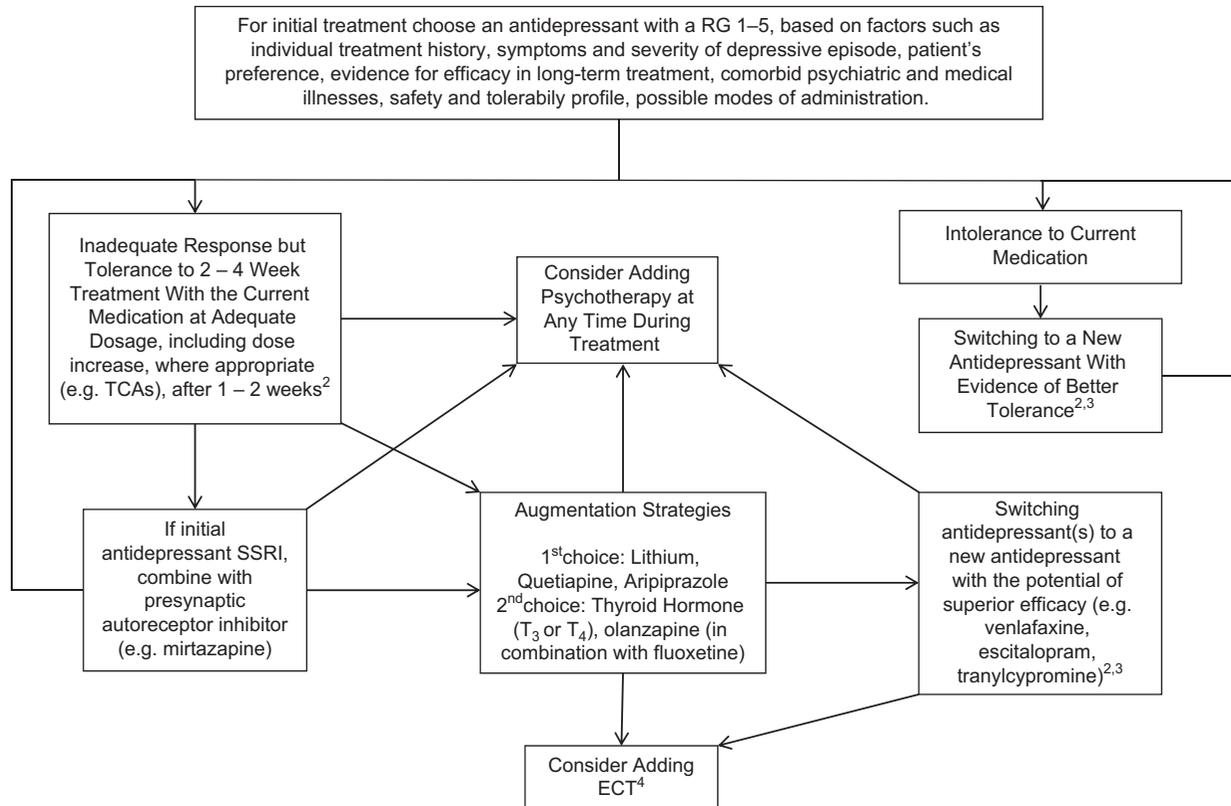> be monitored.
>
> CE B, RG 3

Figure 3. Flow chart – therapeutic options in partial and nonresponders[1] to initial treatment with an antidepressant in major depressive disorder.

2.4 Electroconvulsive therapy

Electroconvulsive therapy (ECT) involves an electrical stimulus to elicit a therapeutic, epileptic seizure in the brain. The efficacy of ECT in the treatment of major depressive disorder is well established (Nobler and Sackeim 2000; Fink 2001). A series of randomized controlled trials have demonstrated that ECT is superior to placebo, simulated ECT and antidepressant medication therapy. ECT is associated with a 60–80% remission rate, with maximum response typically achieved after 2–4 weeks. The evidence base includes at least two clinical trials, three reviews with secondary data analysis (UK ECT Group 2003; Husain et al. 2004; Pagnin et al. 2004; Prudic et al. 2004; Greenhalgh et al. 2005), for psychosis one clinical trial (Petrides et al. 2001), for atypical features one clinical trial (Husain et al. 2008) and for melancholic features one clinical trial (Fink et al. 2007). For patients whose symptoms have not responded adequately to medication, ECT remains the most effective form of therapy (Prudic et al. 1996; Dombrovski et al. 2005; Rasmussen et al. 2007).

WFSBP recommendation:

> Among the indications for Electroconvulsive therapy (ECT) as a first-line treatment are: severe major depression with psychotic features, severe major depression with psychomotor retardation, "true" treatment-resistant major depression, refusal of food intake or in other special situations when rapid relief from depression is required (e.g., in severe suicidality) or medication contraindicated (e.g., in pregnancy). ECT as a first-line approach may also be indicated in patients who have experienced a previous positive response to ECT, and in patients who prefer ECT for a specific reason.
>
> CE C, RG 4

ECT is increasingly combined with antidepressants to improve acute-phase response, although as yet little data exists supporting this practice (APA 2000). One disadvantage of ECT is that its effects only last for a few months without follow-up treatment. The relapse rate without continuation

treatment has been estimated to be between 50 and 95% (Bourgon and Kellner 2000), with the majority of the relapses occurring in the first 6 months. In a controlled study of the post-ECT phase, paroxetine was shown to be superior to both imipramine and placebo in preventing relapse (Lauritzen et al. 1996). A well conducted study by Sackeim et al. (2001) demonstrated that nortriptyline is more effective than placebo, and the combination of nortriyptyline plus lithium is more effective than nortriptyline alone in preventing early relapse after successful ECT. Medication resistance and greater severity of depression pre-ECT has also been shown to predict relapse. Thus, medication used unsuccessfully prior to ECT cannot be recommended to prevent post-ECT relapse (Bourgon and Kellner 2000; Nobler and Sackeim 2000).

Other drawbacks of ECT are the transient postictal confusional state and a period of anterograde and retrograde memory impairment which, in most cases, resolve after a short period of time (Nobler and Sackeim 2000). In general, ECT is a safe procedure, and, apart from raised intracranial pressure, there are no absolute contraindications to ECT.

WFSBP recommendation:

> Prior to ECT treatment implementation, a thorough medical evaluation of the patient must be performed in close collaboration with an anaesthesiologist. Caution is indicated in patients with evidence of increased intracranial pressure or cerebrovascular fragility, in patients with cardiovascular disease, e.g., recent myocardial infarction, myocardial ischaemia, congestive heart failure, cardiac arrhythmias or pacemakers, or abdominal aneurysm and in patients with severe osteoporosis.[1] ECT may only be performed by a psychiatrist who is experienced with this treatment intervention.
>
> Clinical consensus

[1]APA (2000).

ECT is generally well tolerated with an estimated adverse-event rate of about 0.4% (Kennedy et al. 2001). The most common side effects are objective cognitive impairment (typically transient retrograde amnesia that lessens during a period of several weeks post-ECT) and subjective impairment of (autobiographical) memory. ECT can also cause a transient rise in heart rate, blood pressure and intracranial pressure. Rare side effects include headaches, muscle aches and nausea (Datto 2000; Nobler and Sackeim 2000). A comprehensive review concluded that there is no reliable evidence that ECT causes structural brain damage (Devanand 1995).

ECT is typically conducted on inpatients, but outpatient (ambulatory) ECT practice is growing, largely because of its increasing use for continuation and maintenance treatment (see Part 2 of these guidelines). Treatments are usually administered every other day, three times a week, or twice a week in some countries. Less frequent administration produces less cognitive impairment but has not been shown to be as effective. Unilateral ECT produces less memory impairment than bilateral ECT, but treatment may be less effective in some patients (Sackeim et al. 1993; Sackeim et al. 2000). Unilateral electrode placement requires an energy six times the seizure threshold (defined as the lowest energy necessary to produce adequate generalized seizure) to have the same efficacy as bilateral placement (Sackeim et al. 1987, 2000). Ideally, the total course of treatment should aim for remission of the depression and typically involves six to 12 treatments. It rarely exceeds 20 treatments.

2.5 Psychotherapy

Up to now, research in psychotherapy has been hampered by the fact that placebo psychotherapy does not exist as, similar to the placebo effect in clinical practice, every interaction between humans, e.g., in psychotherapy, is inevitably embedded in a psychosocial context which has a specific meaning and gives rise to distinct expectations in the individuals involved (patient, psychotherapist) – and can therefore, by definition, not be inactive. Furthermore, blinding psychotherapeutic approaches, in contrast to psychopharmacological treatment approaches, has not been feasible. Consequently, establishing the proof of efficacy in a methodologically comparable way to psychopharmacological interventions (double-blind, placebo-controlled trials) has been impossible (Hegerl et al. 2012).

Having said this, and while not the main focus of this guideline, psychotherapy plays an important part in the management of depressed patients. Psychotherapy involves a learning process in which a depressed person works with a health professional to learn skills that can help the patient overcome symptoms of depression.

Brief, structured psychotherapy sessions have been shown to be effective in the acute-phase treatment of major depression (Frank et al. 2000) and in preventing relapse in the continuation-phase treatment (Jarrett et al. 2001). These therapies tend to be time-limited (6–20 sessions) and focus on current problems rather than on the past. They emphasize patient education about depression and involve an active collaboration of patients and therapists.

The best studied psychotherapies efficacious for depression include: cognitive behavioural therapy (CBT; Rush et al. 1977; Beck et al. 1979; Dobson 1989; Hollon et al. 1992; Gaffan et al. 1995; Blackburn and Moore 1997; Gloaguen et al. 1998; DeRubeis et al. 1999; Petersen et al. 2004), behavioural therapy (Rehm 1979; Bellack et al. 1983; Lewinsohn and Clarke 1984; Nezu 1986; AHCPR 1993; Jarrett and Rush 1994), interpersonal therapy (IPT; Klerman et al. 1984; Elkin et al. 1989; Schulberg et al. 1996; Markowitz 2003) and the cognitive behavioural analysis system of psychotherapy (CBASP; McCullough 2000; McCullough 2003). However, a recent meta-analysis (Jakobsen et al. 2012) of cognitive therapy concluded that effectiveness in reducing depression severity might be overestimated because of bias and random effects, and that the overall benefit in terms of remission, suicidality, adverse events and quality of life remains unclear.

Several of the mentioned forms of psychotherapy also appear effective in elderly depressed patients (Hautzinger and Welz 2004; systematic review Hollon et al. 2005).

There is less empirical evidence for the efficacy of other types of psychotherapy (for example psychodynamic psychotherapy), while this does not exclude that such treatments are effective, they cannot be recommended on current evidence.

Problem solving treatment (PST) has been shown to be an effective treatment for depressive disorders in primary care compared to placebo in one study (Mynors-Wallis et al. 1995) but not in a second subsequent study (Mynors-Wallis et al. 2000). In reducing depressive symptoms in elderly people, PST is also an effective treatment option (Alexopoulos et al. 2003). PST can be delivered by non-specialists after training and could, therefore, be a cost-effective alternative to formal psychotherapy.

Pharmacotherapy can be combined with psychotherapy (a) initially when treatment is started, (b) when a depressed patient does not respond or only partially responds to treatment with an antidepressant, or (c) when a depressed patient does not respond to initial psychotherapy as monotherapy (Paykel et al. 1999; Frank et al. 2000; Scott 2000; Rush and Kupfer 2001). The potential benefits of combining pharmacotherapy with psychotherapy include improved treatment response, reduced relapse rates, enhanced quality of life, and increased adherence to pharmacotherapy (Segal et al. 2001). Although widely used in clinical practice, the evidence to support such an approach is inconsistent (de Jonghe et al. 2001, 2004; Burnand et al. 2002; Jindal and Thase 2003; see also Keller et al. 2000 for efficacy in chronic depression).

WFSBP recommendation:

> Psychotherapy should be considered as an initial treatment modality for patients with mild depression. Furthermore, psychotherapy is recommended in combination with antidepressants for patients with moderate to severe depression and for patients who have had only partial responses to antidepressant medications or who have had problems with adherence to antidepressants.[1] Patient preference for antidepressant medications or psychotherapy and the availability of psychotherapy should be considered when deciding between initiating treatment with antidepressant medications or psychotherapy.
>
> CE B, RG 3

[1]Rush and Thase (1999).

2.6 Light therapy

Seasonal affective disorder (SAD) is a distinct subtype of recurrent major depression that manifests with a seasonal pattern (Rosenthal et al. 1984; APA 1994). It is estimated that about 5–10% of the general population, predominantly women, are affected (Kasper et al. 1989; Rosen et al. 1990). "Winter" depression is the most common type of SAD in which patients experience symptoms of clinical depression during the fall and winter, with full remission during the spring and summer seasons.

The preferred device for light therapy is a fluorescent light box (which provides white, fluorescent light with ultraviolet wavelengths filtered out) that produces light intensities greater than 2,500 lux. The starting "dose" for light therapy is 10,000 lux for 30–40 min per day, administered each morning for a 2–4-week period. Alternatively, light boxes emitting 2,500 lux require 2 h of exposure per day (Lam and Levitt 1999). Correct positioning (seated close enough to the light box, i.e. no more than 50–80 cm apart, eyes opened) is important. Patients usually show improvement within 1 week, but it can take up to 4 weeks until the full response is achieved. If a light box is not available, "natural light treatment" may be recommended to patients with SAD by a daily 1-h outdoor morning walk for two or more weeks (Wirz-Justice et al. 1996; Levitt et al. 2002).

There are no absolute contraindications to light therapy and no evidence that it is associated with ocular or retinal damage. However, patients with ocular risk factors should have a pretreatment ophthalmological consultation. The common side effects of light therapy reported by patients in clinical trials include eye strain or visual disturbances, headache, agitation, nausea, sedation and, very rarely, hypomania

or mania. These side effects are generally mild and transient and resolve with time or with reduction of the light dosage (Lam and Levitt 1999).

Regarding efficacy of light therapy the NICE guidelines reviewed a large number of studies stating that they varied considerably in methodology. The intensity and duration of light, time of day, mode of administration of light, and the comparison conditions were different across studies. They concluded that while bright light is clearly more effective than waitlist control, it is unclear if this is more than a placebo effect. Studies that compare bright light with other treatments that are not known to be effective give equivocal results. For details see the NICE guidelines (NICE 2009).

Combining light therapy with an antidepressant may potentiate the efficacy of the treatment. However, potential photosensitizing effects of phenothiazine neuroleptics (e.g., chlorpromazine), tricyclic antidepressants and hypericum should be considered, and patients receiving both treatments should be advised to take appropriate precautions.

A meta-analysis of studies assessing the efficacy of light therapy in *nonseasonal* depression did not find an overall statistically significant difference in treatment response compared to control treatment. However, when selecting only high-quality studies and studies applying morning treatment a superiority of bright light therapy can be established (Cochrane Review: Tuunainen et al. 2004). In a recent 9-week study patients were randomized to either combined wake therapy, bright light therapy and sleep time stabilization or to exercise training, both in combination with duloxetine. The chronotherapy group did show an augmented and sustained antidepressant response and remission compared to patients treated with exercise. (Martiny et al. 2012).

WFSBP recommendation:

> Light therapy is an option in treatment of SAD if administration is possible and protocol adherence can be ensured.
>
> CE B, RG 3

2.7 Adjunctive therapy

Interventions intended to provide complementary effects are referred to as adjunctive therapies (Thase et al. 1998). Pharmacological as well as non-pharmacological adjunctive therapies have been suggested for the treatment of major depression (Marangell 2000). Included below is a review of tranquilizers/anxiolytics, sleep deprivation, and exercise training. Many of these treatments may help to reduce anxiety and insomnia until full recovery is achieved.

2.7.1 Tranquilizers/anxiolytics. Many experts believe that benzodiazepines, in general, do not considerably affect the mood state. Yet, a recent review reported rates for co-administration of an antidepressant and a tranquilizer between 30 and 60% of depressed patients in most countries (Furukawa et al. 2001; Valenstein et al. 2004). The reason for this widespread use is most likely the fast reduction of anxiety, agitation and insomnia in many patients, given the high rate (between 33 and 85% across studies) of anxiety co-morbidity among patients with major depression. In a systematic review, Furukawa et al. (2001) showed that patients with combination treatment of antidepressants and anxiolytics were more likely to show response at 1 and 4 weeks of treatment than patients with antidepressant treatment alone (although the difference was no longer significant at 6–8 weeks). The benefits of adding anxiolytics have to be weighed against risk of dependence and proneness to accidents.

WFSBP recommendation:

> In each individual patient the potential benefits of adjunctive treatment with benzodiazepines must be carefully weighed against possible harm (including sedation, psychomotor and cognitive impairment, potentiation of other central nervous system depressants, development of dependence and discontinuation syndromes). In general, benzodiazepines should not be administered to patients with a history of or current alcohol or drug abuse/dependence. It is also recommended that the duration of benzodiazepine administration in depressed patients should be typically restricted to a maximum period of approximately 4–6 weeks until the antidepressant has proved to be effective.
>
> Clinical consensus

2.7.2 Sleep deprivation ("wake therapy"). Total or partial sleep deprivation (SD) may be the only antidepressant intervention, besides ketamine, with marked beneficial same-day effects, providing transient amelioration of depression in about 60% of patients (Kuhs and Tolle 1991; Wirz-Justice and Van den Hoofdakker 1999; Giedke et al. 2003). Sleep deprivation alone, preferentially total SD, is used to treat unmedicated depressed patients, or is started in parallel with antidepressant medication to accelerate the response to medication. It can also be added to potentiate an ongoing antidepressant drug therapy (Van den Hoofdakker 1994; Kuhs et al. 1996). SD response is most pronounced in those patients manifesting daily and day-to-day variability of mood (Wirz-Justice and Van den Hoofdakker 1999). It is

an attractive adjunctive treatment for major depression because it works rapidly and is noninvasive, inexpensive, and well tolerated by the majority of patients. However, most patients who do respond subsequently relapse after one night of sleep (Wu and Bunney 1990; Giedke and Schwarzler 2002). Usually, the antidepressant effect can be replicated by repeated total sleep deprivation (Wiegand et al. 2001) or by combining sleep deprivation with subsequent phase advance of the sleep period (Riemann et al. 1999). Bright light therapy has been shown to stabilize the antidepressant effect of partial sleep deprivation (Neumeister et al. 1996). Other strategies to sustain the antidepressant effect include combining SD with lithium, pindolol, or thyroid hormone (Wirz-Justice and Van den Hoofdakker 1999).

As mentioned above, in a recent 9-week study patients were randomized to combined wake therapy, bright light therapy and sleep time stabilization or to exercise training, both in combination with duloxetine. The chronotherapy group showed an augmented and sustained antidepressant response and remission compared to patients treated with exercise (Martiny et al. 2012).

WFSBP recommendation:

> Sleep deprivation alone, preferentially total SD, may be used to treat unmedicated depressed patients, or be started at the same time as an antidepressant medication with the goal of accelerating the response to medication. It may also be added as a strategy to potentiate an ongoing antidepressant drug therapy.
>
> CE C1, RG 4

2.7.3 Exercise training. Studies of healthy young people have shown that physical activity may have positive effects on mood. Open studies of short-term effects of an adjunctive daily aerobic exercise program suggested relatively rapid (after 14 days) mood improvements in patients with major depression (Dimeo et al. 2001). A critical review on this treatment option discusses the potential mechanism of action of exercise (Brosse et al. 2002). The effectiveness of this treatment strategy could not be analysed in an early meta-analysis because of a lack of good quality studies (Lawlor and Hopker 2001). In a randomized, placebo-controlled study published since that review, significant antidepressant effects of strenuous walking were shown in 38 depressed patients Knubben et al. (2007). In a new Cochrane meta-analysis, the authors concluded that "exercise seems to improve depressive symptoms in people with a diagnosis of depression when compared with no treatment or control intervention, however since

analyses of methodologically robust trials show a much smaller effect in favour of exercise, some caution is required in interpreting these results" (Mead et al. 2008).

WFSBP recommendation:

> Exercise training can be used as an adjunct to medication treatment for patients with mild to moderate depression.
>
> CE B, RG 3

2.8 Other treatment options

2.8.1 Transcranial magnetic stimulation (TMS). TMS works via noninvasively stimulating cortical neurons by magnetic induction, using a brief, high-intensity magnetic field (Pascual-Leone et al. 1996; George et al. 1999; McNamara et al. 2001). Studies evaluating the efficacy of rTMS are heterogeneous regarding the frequency and location of stimulation and show inconsistent results. A recent meta-analysis showed a small benefit immediately after 2-week treatment trials compared to sham treatment (Martin et al. 2003).

The side effects and the long-term changes in brain function potentially associated with rTMS are largely unexplored. Open-label reports on maintenance rTMS suggest that it has long-term safety (CANMAT 2009). Provocation of epileptic seizures has been described in rare cases (Loo et al. 2008).

Growing evidence suggests that the combined use of rTMS with antidepressant medication accelerates response under sham-controlled conditions, although initial advantages are not always sustained. Adding open-label mirtazapine also increased the response to rTMS monotherapy. The evidence for the combination treatment is based on the following studies: Bretlau et al. (2008), Rossini et al. (2005a, 2005b), Rumi et al. (2005), Poulet et al. (2004), and Schule et al. (2003).

WFSBP recommendation:

> There is currently insufficient evidence for the clinical efficacy that allows to recommend TMS in the standard clinical setting. Further research is needed.
>
> CE D, RG 5

2.8.2 Vagus nerve stimulation (VNS). VNS stimulates the brain indirectly via the vagus nerve (cranial nerve X). A generator about the size of a pocket watch is implanted subcutaneously into the left chest wall and is connected to bipolar electrodes that are attached to the left vagus nerve within the neck.

Theoretically, activation of the vagus nerve may improve mood via its ascending projections to the amygdala and other limbic structures known to influence emotion and mood (George et al. 2000). Data from a sham-controlled trial essentially show no difference in response after 10 weeks but increasing response rates for VNS over 1 year; however, the increased response rates over these 12 months were uncontrolled (George et al. 2005; Rush et al. 2005). The overall evidence base consists of a maximum of 1,855 patients from one systematic review (Daban et al. 2008), two randomized controlled trials (Nahas et al. 2007; Nierenberg et al. 2008), one non-randomized controlled trial (Sperling et al. 2009), and three case series (Sackeim et al. 2007; Franzini et al. 2008; Schlaepfer et al. 2008).

WFSBP recommendation:

> VNS may be an option in patients with depression with insufficient response to trials of pharmacotherapy.
>
> CE D, RG 5

See Figure 3 mentioned before for a flow chart on therapeutic options in partial and non-responders to initial treatment with an antidepressant.

2.9 Treatment-Resistant Depression (TRD)

As many as 50% of non-responders to a first antidepressant trial also fail to respond to a second, different course of treatment. This residual group of patients remains depressed and does not achieve adequate relief and a satisfactory level of functioning even after two or more adequate courses of treatment.

There is no universally accepted definition of treatment resistance. In a systematic review, Ruhe et al. (2012) critically discussed five staging models: the Antidepressant Treatment History Form (ATHF; Sackeim et al. 1990; Oquendo et al. 2003), the Thase and Rush Model (TRM; Thase and Rush 1997), the European Staging Model (ESM; Souery et al. 1999), the Massachusetts General Hospital Staging Model (MGH-s; Fava 2003) and the Maudsley Staging Model (MSM; Fekadu et al. 2009b, Table V). The MSM summarizes the actual stage of TRD in a single score, varying between 3 and 15. It incorporates duration and severity of the MDD episode. Staging of TRD can also be presented in three ordinal categories: mild (scores = 3–6), moderate (scores = 7–10) and severe (scores = 11–15). For this model, the predictive value was the highest, it correctly predicted treatment resistance in 85.5% of the cases (Fekadu et al. 2009b). Higher MSM scores were found to predict the persistence of a depressive episode throughout follow-up of a median of 30 months (Fekadu et al. 2009a). Despite this, Ruhe et al. (209, 2012) argue that further investigation of the reliability and predictive utility of TRD staging models and additional disease characteristics is required. Regulatory agencies define TRD as

Table V. Maudsley staging parameters and suggested scoring conventions (MSM).

Parameter/Dimension	Parameter specification	Score
Duration	Acute (≤ 12 months)	1
	Sub-acute (13–24 months)	2
	Chronic (< 24 months)	3
Symptom severity (at baseline)	Subsyndromal	1
	Syndromal	
	–Mild	2
	–Moderate	3
	–Severe without psychosis	4
	–Severe with psychosis	5
Treatment failures (antidepressants)[1]	Level 1: 1–2 medications	1
	Level 2: 3–4 medications	2
	Level 3: 5–6 medications	3
	Level 4: 7–10 medications	4
	Level 5: > 10 medications	5
Augmentation	Not used	0
	Used	1
Electroconvulsive therapy	Not used	0
	Used	1
Total		3–15

[1]Antidepressant trials only count when given for ≥ 6 weeks at adequate doses.

depression that failed to show clinically meaningful improvement after treatment with at least two different antidepressant agents prescribed in adequate dosages for adequate duration and with adequate affirmation of treatment adherence (EMA 2011).

While many of the non-responders to initial treatment may improve with the treatment strategies that have been described above, some of these patients develop a chronic course of the illness (Scott 1988; Thase and Rush 1995).

It has been suggested that inadequately performed pharmacotherapy and unsystematic treatment plans may contribute to this unfavourable treatment outcome. In clinical practice, treatment-resistance frequently results from inadequate dosage and inappropriate length of treatment with antidepressants or from insufficient use of the available therapeutic repertoire in case of incomplete response (Nierenberg and Amsterdam 1990; Guscott and Grof 1991; Montgomery 1991; Bauer and Helmchen 2000). Some studies indicate that only a minority of patients labeled "treatment-resistant" are "absolutely" resistant, the majority of "relative" resistors can be helped substantially by rigorous treatment approaches including a course of electroconvulsive therapy (ECT). Patients with a history of positive response to ECT may be candidates for immediate ECT when a new episode requires treatment.

Repeated inadequate drug trials may be harmful to the patient and may contribute to a negative outcome of the depression. Some evidence exists that repeated drug trials per se are associated with treatment-resistant depression (Amsterdam and Hornig-Rohan 1996). Data have suggested that the probability of responding to an antidepressant declines by a factor of approximately 15–20% for each prior failed drug treatment (Amsterdam et al. 1994). As mentioned before, the assumption behind the development of systematic treatment approaches (algorithms) is that decreasing the variance and increasing the appropriateness of treatment strategies results in enhanced patient outcomes and avoidance of development of refractoriness (Amsterdam and Hornig-Rohan 1996; Gilbert et al. 1998; Rush et al. 1998; Rush 1999). Treatment algorithms are key instruments aimed at improving adherence to antidepressant regimens and in optimizing the execution of treatment in terms of treatment effectiveness and cost efficiency. See Section 2.1 for examples.

Other reasons for treatment resistance include "hidden bipolarity" (Dudek et al. 2010).

3. Continuation-phase treatment of major depressive disorder

The objective of continuation treatment is to decrease the likelihood of relapse during the vulnerable period following symptomatic recovery from depression (i.e. to prevent a return of the current episode of depression) (AHCPR 1993). The continuation phase of treatment is generally considered as a 6-month period of time immediately following full remission. However, some authors recommend continued treatment for up to 9 months (Reimherr et al. 1998; Hirschfeld 2001; Rush and Kupfer 2001). In general, patients with a history of long previous episodes are candidates for continuation-phase treatment of more than 9 months (Rush and Kupfer 2001). Because residual symptoms (partial remission) are strong predictors of subsequent early relapse, it is recommended to continue treatment until such symptoms have subsided (Paykel et al. 1995). Psychotherapy may be added to continuation medication if residual depressive symptoms are not ameliorated by medication alone (Fava et al. 1998; Rush and Kupfer 2001). Continuation-phase treatment for psychotic depression should last longer than the treatment of non-psychotic depression (REF).

WFSBP recommendation:

> The continuation phase of treatment lasts at least 6 months following remission of the acute symptomatology. Treatment should be prolonged to 9 months in patients with a history of long previous episodes and should continue even longer in cases of residual symptomatology and until such symptoms have subsided and in psychotic depression.
>
> Clinical consensus

In placebo-controlled continuation therapy trials, mostly with TCA, relapse rates ranged from 31 to 80% for those patients who received placebo, compared with only 0 to 31% of those who received active medication (Prien and Kupfer 1986; Prien 1990; Geddes et al. 2003). Later continuation-phase studies involving SSRI, amineptine, nefazodone, and reboxetine showed similar results (Hirschfeld 2001). In these latter studies, 33 to 56% of the patients who did not continue active medication after stabilization (i.e. were switched to placebo) relapsed, whereas only 7 to 26% of those who continued on active medication relapsed (Hirschfeld 2001).

WFSBP recommendation:

> It is recommended that the same antidepressant successfully used to achieve response/remission in the acute-phase therapy should be continued at the same dose during the *continuation phase*.[1] If no relapse occurs during continuation therapy, a gradual discontinuation of the antidepressant medication is recommended in case of first episodes.[2] Patients should be carefully monitored during and immediately after discontinuation to ensure the stability of the remission.[3] If tapering off results in a return of symptoms, the medication should be re-instated in the original dose for at least another 6 months before attempting discontinuation again.
>
> CE B, RG 3

[1]Thase (1999), Rush and Kupfer (2001). [2]Rosenbaum et al. (1998), [3]APA (2000).

There are a limited number of controlled trials of augmentation strategies or additional ECT treatment administered in the continuation phase. These few studies indicate that ECT treatment in addition to antidepressants is more efficacious during the continuation phase than the use of antidepressant treatment alone (Gagne et al. 2000).

Following a successful course of acute-phase lithium augmentation, combined continuation treatment using an antidepressant and lithium is superior to the combination of an antidepressant and placebo (Bauer et al. 2000; Bschor et al. 2002). In another continuation treatment study, nortriptyline-lithium combination following ECT had a marked advantage for time to relapse, superior to both placebo and nortriptyline treatment alone (Sackeim et al. 2001).

4. Treatment in special circumstances

Under special circumstances, the treatment of depression needs to be modified. These circumstances include depression co-occurring with other psychiatric conditions (anxiety disorders, substance abuse, or dependencies), depression in older adults, depression due to a general medical condition and depression during pregnancy and breast-feeding.

4.1 Co-morbidity of depression with other psychiatric disorders

4.1.1 Co-morbid anxiety disorders. Many patients with depression have symptoms of anxiety (anxious depression) (Wiethoff et al. 2010), and up to 30% suffer from additional anxiety disorders including panic disorder and posttraumatic stress disorder (PTSD; Wittchen et al. 1999).

Effective treatment of co-morbid depression and anxiety necessitates the use of medications that demonstrated efficacy for both conditions (Bakish 1999; Schatzberg 2000).

WFSBP recommendation:

> Depressed patients with prominent symptoms of anxiety or with co-morbid anxiety disorders such as panic disorder, generalized anxiety disorder, or PTSD, can be treated effectively with the SSRI or venlafaxine[1] or TCAs or MAOIs, but medications should be initiated at low doses (for example 5 mg of fluoxetine or 10 mg of paroxetine) and increased slowly to full therapeutic doses. Rapid titration could cause a transient worsening of anxiety symptoms before anxiety and depression respond to the intervention.
>
> CE C1, RG 4

[1]Fawcett and Barkin (1998), Rudolph et al. (1998), Schneier et al. (2003), Brady and Clary (2003).

WFSBP recommendation:

> Cognitive behavioural psychotherapy (CBT) and Interpersonal psychotherapy (IPT) have also demonstrated efficacy in the treatment of co-morbid anxiety symptoms.[1]
>
> CE B, RG 3

[1]APA (2009), Ninan et al. (2002).

In some cases, the use of a benzodiazepine such as diazepam, lorazepam, or clonazepam is helpful to reduce severe anxiety during the initial weeks of treatment.

WFSBP recommendation:

> During the initial weeks of treatment benzodiazepines may prove helpful in cases of depression with symptoms of anxiety or comorbid anxiety disorders.
>
> CE A, RG 1

WFSBP recommendation:

> The use of benzodiazepines in the long-term treatment of depression with co-morbid anxiety is strongly discouraged because of the risks of tolerance, cognitive, and motor impairment as well as psychological and physical dependence.
>
> Clinical consensus

4.1.2 Co-morbid obsessive–compulsive symptoms and disorders (OCD). Obsessive–compulsive symptoms

and disorders are also common in patients with MDD. Clomipramine and SSRI, e.g., fluoxetine and paroxetine, have demonstrated efficacy in the treatment of OCD and MDD (Pigott and Seay 1999; Schatzberg 2000; Koran et al. 2007).

WFSBP recommendation:

> Clomipramine and SSRIs are recommended for treating depressed patients who have obsessive–compulsive symptoms or co-morbid OCD.
>
> SSRI doses for obsessive–compulsive symptoms and co-morbid OCD are typically higher (2–3 times) than the treatment doses for depression.
>
> CE A, RG 2

4.1.3 Substance abuse or dependence. Depressive syndromes and substance abuse are frequently intertwined. Research has highlighted the high prevalence (30–60%) of co-morbid mood and anxiety disorders in patients with substance abuse/dependency with secondary depression being more frequent than primary depression (12–51 and 2–12% of alcohol addicts, respectively, Soyka and Lieb 2004). Similarly, at least a third of those with affective disorder report a history of substance abuse/dependency (Regier et al. 1993; Scott et al. 1998).

Due to the clinical complexity of the presentation, it is often not easy to differentiate primary from secondary mood disorder resulting from misuse/dependence. With primary mood disorder, depressive symptomatology precedes substance misuse.

4.1.3.1 Primary mood disorder. Patients with major depression are at increased risk for the use of alcohol, illicit drugs, or prescription drugs (Schuckit 1994). The presence of such substance abuse in patients with depression has important implications for the treatment of depression. Substance abuse can threaten the person's adherence to treatments for depression and reduce the effectiveness of depression treatments. In addition, both diseases are associated with an increased risk for suicide.

Persons who have depression and also abuse substances require simultaneous treatment for both problems because it is rarely sufficient to treat the depression alone.

Treatment options for substance abuse vary widely. It is important to be aware of additional local treatment options such as self-help groups.

> In case of significant co-morbid active substance abuse it is prudent to initiate treatment for substance abuse before starting an antidepressant because symptoms of depression may remit with successful treatment of the substance abuse. Attention has to be paid to possible interactions with the prescribed drug.
>
> Clinical consensus

Pharmacokinetic interactions from the concurrent use of methadone and antidepressants (e.g., amitriptyline) may lead to respiratory depression and sedation. According to the APA guidelines, co-occurring substance use, especially with stimulant drugs, raises the risk of deleterious interactions with MAOIs, although few such events have been reported (Sands and Ciraulo 1992). Benzodiazepines and other sedative hypnotics carry the potential for abuse or dependence and should rarely be prescribed to patients with co-occurring substance use disorders, except as part of a brief detoxification regimen. Hepatic dysfunction and hepatic enzyme induction frequently complicate pharmacotherapy of patients with alcoholism and other substance abuse. These conditions may require careful monitoring of blood levels (as appropriate for the medication), therapeutic effects, and side effects to avoid the opposing risks of either psychotropic medication intoxication or underdosing.

4.1.3.2 Substance-induced mood disorder. DSM-IV (APA 1994) defines substance-induced mood disorder as the prominent and persistent disturbance in mood judged to be due to the direct physiological effects of a substance.

WFSBP recommendation:

> Although antidepressant pharmacotherapy may have a role in the treatment of severe substance-induced mood disorders, the benefits of using these medications must be weighed against the increased risk of side-effects or adverse reactions in individuals who continue to engage in substance use or who have medical complications associated with substance use.* Effective psychosocial approaches focus largely on brief, empirically tested treatments, such as cognitive therapy. However, modifications to such approaches are required to ensure that the interventions are tailored to the needs of patients exhibiting substance use and mood disorder.[1]
>
> Clinical consensus

[1]Scott et al. (1998).

4.2 Treatment of depression in older adults

MDD in late life is more prevalent than previously reported. If left untreated MDD in later life is associated with a poor prognosis (Cole et al. 1999; Katona 2000; Steffens et al. 2000;Whyte et al. 2004). There are particular challenges in treating older people with MDD effectively and safely. Pathophysiology in old age may be different (e.g., vascular depression), changes in physiology associated with advancing age produce clinically significant differences in drug metabolism and pharmacokinetics in older versus younger adult patients (Rabheru 2004). Older adults are also more likely to require and receive treatment for co-morbid somatic illnesses, which increases the potential for serious pharmacodynamic and pharmacokinetic drug–drug interactions (Preskorn 1993; Dunner 2003).

There is relatively little data on the use of antidepressants in older patients, especially in the very old (>75 years) and in those with significant medical co-morbidity, dementia, or neurological problems (Flint 1998; Roose and Suthers 1998; Roose et al. 2004). In a recent meta-analysis of all studied antidepressants, Tedeschini et al. (2011) found substantial heterogeneity between studies. It seems that while antidepressants were not significantly more efficacious compared to placebo in patients 65 years and older, they were in trials where the age threshold for inclusion had been set to 55 years, especially when non-elderly patients aged below 65 years were included in the study. The authors discuss potential reasons for this finding, e.g., greater chronicity and lower doses used. Discontinuation rates were not significantly different compared to placebo independent of age ($n = 15$ trials with age ≥ 55; of that $n = 6$ with age ≥ 65 (of that only one with age ≥ 75); $n = 59$ with age < 65; Tedeschini et al. 2011).

Compared to young adults, response to antidepressant treatment may be slower in older adults (this holds true for "older" antidepressants (Katona 1994), whereas there is conflicting data regarding "newer" ones (Sackeim et al. 2005; Nelson et al. 2008).

Older patients demonstrated a higher relapse rate during continuation-phase treatment (Reynolds et al. 1996). In a meta-analysis including data from eight RCTs of a systematic review Kok et al. (2011) found that continuing treatment with antidepressants after remission in the elderly was more efficacious than placebo (with a NNT of 3.6 (95% CI 2.8–4.8) for preventing one additional relapse or recurrence). There was no significant difference in efficacy of TCA vs. SSRI (NNT 2.9 vs. 4.2). Interestingly, study drop-out rate due to side effects was low (4.1%) compared to rates found in younger adults (around 7%) and in acute treatment studies (18–24%). (Kok et al. 2011).

Regarding unwanted effects, cardiovascular side effects are a particular concern in older adults. In a trial comparing paroxetine with nortriptyline use for treatment of depressed patients with ischaemic heart disease, including a considerable proportion of patients older than 60, the two drugs were equally effective for depression, but nortriptyline was associated with a significantly higher rate of serious cardiac adverse effects (Roose et al. 1998). Anticholinergic adverse events (e.g., cognitive impairment, constipation, urinary retention) are another important issue in the older population.

Due to missing significant differences in efficacy of the various classes of antidepressants, choice of medication is determined mainly by comparing side effect profiles. Interestingly, in a recently published population based cohort study of 54,038 elderly patients (65 + years of age) with depression, Coupland et al. (2011) found significant differences in associations of different antidepressant drug classes and adverse outcomes. Patients who received SSRI after being diagnosed with depression had a higher hazard ratio vs. treatment without antidepressant compared to treatment with TCA for all-cause mortality, stroke/TIA, fracture, seizures and hyponatraemia (but not for attempted suicide). Hazard ratios were higher compared to TCA in patients with "other" antidepressants (mirtazapine, venlafaxine) for all-cause mortality, attempted suicide, stroke/TIA, fracture and seizures (but not for falls and hyponatraemia). For most outcomes, the risk was highest in the first 4 weeks after beginning and stopping treatment. The authors discuss possible explanations, including the frequent use of low dosages of TCA (Coupland et al. 2011).

Data from new antidepressant agents studied in elderly patients (Katona et al. 2012) have to be substantiated.

WFSBP recommendation:

> MDD in later life is thought to be underdiagnosed and undertreated, there is insufficient data to precisely estimate the efficacy of antidepressants in patients aged 65 years and older.
>
> Also in elderly patients, continuation-phase treatment proved efficacious compared to placebo.
>
> EC B, RG 3

WFSBP recommendation:

> In spite of insufficient data regarding the precise efficacy of antidepressants in the elderly, old age should not per se limit the full use of the whole spectrum of antidepressant options.
>
> Clinical consensus

WFSBP recommendation:

> Older patients are more prone to orthostatic hypotension and more sensitive to other adverse events such as cardiovascular and anticholinergic effects. Therefore, SSRI and the other/newer antidepressants are generally preferred over TCA. However, recent evidence for higher risk for unwanted outcomes with these newer antidepressants has to be considered and reappraised.[1]
>
> Older patients are typically started on a lower oral dose than younger adult patients, but it may be necessary to titrate doses for effectiveness. Higher plasma concentrations for a given dose are generally found in older compared to younger individuals[2] and doses may need to be adjusted particularly in patients with impaired renal or liver function.
>
> Clinical consensus

[1]Coupland et al. (2011), [2]Anderson et al. (2000).

Cooper et al. (2011) systematically reviewed the evidence for inadequate and treatment-resistant depression in elderly patients. They found only three randomized studies including one placebo-controlled trial (one open, Kok et al. 2007: lithium augmentation vs. phenelzine; one single-blind, Mazeh et al. 2007: venlafaxine vs. paroxetine; one double-blind, Sunderland et al. 1994: selegiline vs. placebo) and 10 open-label uncontrolled studies. Lithium augmentation was the only strategy studied in two trials. Overall, half of the elderly patients responded to either the addition of a second agent or a change to another antidepressant (Cooper et al. 2011).

For guidelines on the management of late-life depression under primary care conditions see Baldwin et al. (2003). For treatment of dysthymia in older patients see Part 2 of these guidelines.

4.3 Depression due to a general medical condition

A variety of nonpsychiatric medical conditions may cause symptoms of depression or a major depressive episode. Per DSM-IV, a "mood disorder (depression) due to a general medical condition" is present when a prominent and persistent disturbance in mood (depressed mood) predominates, and when there is evidence from the medical history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition. These conditions include:

- degenerative neurological diseases (e.g., Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease),
- cerebrovascular diseases (e.g., stroke),
- other neurological diseases (e.g., epilepsy, brain tumors),
- endocrine diseases (hypo- and hyperthyroidism, hypo- and hyperadrenocorticism, hypo- and hyperparathyroidism, diabetes mellitus),
- metabolic conditions (e.g., vitamin B12 and folic acid deficiency),
- systemic autoimmune diseases (e.g., lupus erythematosus),
- viral and other infections (e.g., HIV, hepatitis), and
- certain cancers (e.g., cancer of the pancreas and lung).

The incidence of depression during the course of medical conditions (e.g., myocardial infarction, cancer, diabetes mellitus) is about 25%, and as high as 40–50% in patients with neurological disorders (AHCPR 1993; Devanand 1996; Allain et al. 2000). Higher rates of depression may apply in patients with medical conditions directly involving the CNS (e.g., 60% of patients with Cushing's disease). Depression frequently has a poor outcome and patients often have an increased morbidity and mortality. Misdiagnosis and under-treatment of depressive disorder in the physically ill often occurs in clinical practice (Perez-Stable et al. 1990; Üstün and Sartorius 1995).

The general strategy in such cases is to treat the medical condition first, since depression can be an unwanted direct effect of either the illness, or its treatment (AHCPR 1993). If the major depression persists, treatment with an antidepressant is indicated. However, in some cases, major depression is so severe that treatment with an antidepressant should be initiated during the treatment of the medical illness. For patients with "reactive" depressive disorders, additional psychotherapeutic interventions seem appropriate.

A review of 18 randomized studies covering a wide range of physical diseases showed that treatment with antidepressants significantly caused improvement in depression compared to either placebo or no treatment (Gill and Hatcher 2000). There are an

insufficient number of high-quality studies to recommend one medication on the basis of efficacy data over another for the treatment of depressed patients with a concurrent physical illness. The side effect and pharmacological profiles of the antidepressant, patient age, prior response to a specific antidepressant, and potential drug–drug interactions are among the factors that must be considered when choosing a particular antidepressant and its dosages (AHCPR 1993).

Post-stroke depression is probably the best-studied condition in this respect. In placebo-controlled studies, nortriptyline has been superior to placebo (Lipsey and Robinson 1984; Robinson et al. 2000), and to fluoxetine in the treatment of post-stroke depression (Robinson et al. 2000). Citalopram was more effective compared to placebo in a 6-week post-stroke study (Andersen et al. 1994).

Depressive symptoms are common in Alzheimer's disease, but severe depression is less frequent. Four placebo-controlled trials with antidepressants have been carried out in elderly patients with depression and Alzheimer's disease. Three of these studies showed efficacy of clomipramine, citalopram or sertraline (Nyth et al. 1992; Petracca et al. 1996; Lyketsos et al. 2000). A study with imipramine could not find such a difference between the active drug and the placebo (Teri et al. 1991). In a comparator study, paroxetine and imipramine were both effective in the treatment of depression in elderly patients with co-existing dementia, and no significant differences were detected between the groups (Katona et al. 1998). Equal efficacy was also found in a study comparing citalopram with mianserin (Karlsson et al. 2000), and in another comparing fluoxetine with amitriptyline (Taragano et al. 1997). In general, the response rate to SSRI is lower in depressed patients with co-existing dementia than in depressed patients without dementia (reviewed in Enns et al. 2001).

Open-label studies suggest that antidepressants may be effective for treating depression in Parkinson's disease (PD), and although case reports indicate that SSRI can potentially worsen the motor symptoms of PD, this effect has not been confirmed in the small number of open-label studies that have been performed to date (Zesiewicz et al. 1999). In PD with co-morbid depression, either SSRI (sertraline, paroxetine) or moclobemide has been recommended as first-line treatment (Allain et al. 2000). However, the combination of SSRI with the anti-parkinson drug selegiline increases the patients' risk of developing serotonin syndrome. TCAs are not recommended for elderly patients with PD because they can cause delusions and cognitive disorders (Allain et al. 2000).

Drug–drug interactions are important to consider when treating depressed patients with co-morbid illnesses who take nonpsychotropic medications (Table VI; Kent 2000).

For an up-to-date detailed review and guidance on depression with a chronic physical health problem see National Institute for Health & Clinical Excellence (2009).

4.4 Treatment during pregnancy and breast-feeding

Despite the frequency of depression in women of childbearing age (lifetime risk between 10 and 25%), and in pregnant women (about 9%), guidance for patients and physicians is limited. Three primary risks are associated with medication use during pregnancy: (1) teratogenicity, (2) perinatal syndromes (neonatal toxicity), and (3) postnatal behavioural sequelae.

The database for TCA is large and there seems to be no teratogenicity and no increased risk for peri- and postnatal behavioural consequences (Nulman et al. 1997; Simon et al. 2002; Kallen 2004; Davis et al. 2007; Pearson et al. 2007). However, neonatal adaptation difficulties may require intensive care.

Regarding SSRI, the best data-basis is available for citalopram and sertraline suggesting no increased risk for malformations, intrauterine death or major birth defects. For fluoxetine and paroxetine some teratogenic risk has been discussed (increased risk for vascular and heart malformations), therefore these drugs should not be initiated in pregnancy. About a third of the babies delivered to mothers treated with SSRI, especially in the last trimester, show a pattern of symptoms called poor neonatal adaptation (including jitteriness, poor muscle tone, weak or absent cry, respiratory distress with other causes ruled out, hypoglycaemia, low Apgar score and/or seizures; Koren et al. 2005).

For SNRI, the data-basis is still very limited. While, to date, an increased teratogenic risk has not been shown, a higher risk for intrauterine death has been discussed (Tuccori et al. 2009; Nakhai-Pour et al. 2010). Likewise for bupropion, there is still very limited data and no increased teratogenicity has yet been found.

MAO inhibitors are contraindicated during pregnancy due to possible hypertensive crisis.

Use of antidepressants during pregnancy is appropriate in many clinical situations, and should include thoughtful weighing of risk of prenatal exposure versus risk of relapse of the mother following drug discontinuation (risk–benefit decision making). It is of high importance to also involve the partner of the patient into the decision process. Psychotherapy and ECT should be considered as important treatment alternatives. Close monitoring and interventions for

Table VI. Possible interaction of antidepressants with comedications.

Comedication	Interaction
TCAs	
Alpha1-adrenoreceptor antagonists (prazosine)	Heightened decrease of blood pressure
Anesthetics/muscular relaxants (halothane, pancuronium, gallamine)	Heightened risk for arrhythmia
Antazids, adsorbants	Possibly lower AD blood levels
Antiarrhythmics (chinine, lidocaine, disopyramide, procainamide, propafenone)	Prolonged intracardiac conduction times, decreased myocardial contraction up to insufficiency
Anticoagulants (Warfarin, maybe Phenprocoumon)	Heightened effect of anticoagulation with longer bleeding times
Anticonceptives	More side effects of TCA, lower plasma levels of TCA observed, therefore lower antidepressive effect possible
Antidiabetics, oral	Higher plasma levels with increased blood sugar decreasing effect
Antimycotics (fluconazole, ketoconazole)	Higher plasma levels of TCA with more side effects
Beta-Blocker	Heightened decrease of blood pressure, increase of plasma levels of propranolol and TCAs, therefore more side effects, with propranolol possible worsening or induction of depression
Calcium-Antagonists (Diltiazem, Verapamil)	Higher plasma levels of e.g., imipramine, therefore more side effects
Carbamazepine	Risk of lower plasma level of TCA because of induction of enzymes (CYP)
Cimetidine	Higher plasma levels with more side effects
Cisapride	Higher plasma levels of antidepressant with higher risk of side effects
Diuretics	Heightened decrease of blood pressure
Insuline	Possibly increased blood sugar decreasing effect
Nicotine, smoking	Lower blood levels of TCA possible
Omeprazole	Possibly higher plasma levels of TCA with more side effects
Rifampizine	Lower plasma levels of TCA, therefore lower antidepressive effect possible
SSRI	Risk of higher plasma levels of TCA because of inhibition of enzymes (CYP)
SSRI	
Antiarrhythmics (Propafenone, Flecainide)	Inhibition of metabolisation with potentially higher plasma levels of antiarrythmics
Anticoagulants (Phenprocoumon, Warfarin)	Fluvoxamine may increase levels of warfarin. Increased bleeding may result
Antidiabetics, oral	Potentially increased blood sugar decreasing effect of antidiabetics
Antihistaminics (Terfenadine, Astemizole)	Prolongation of intracardiac conduction times and arrhythmias
Beta-Blocker	Inhibition of metabolisation of paroxetine, therefore potentially higher plasma levels with higher risk for side effects
Carbamazepine	Risk of higher plasma level of carbamazepine
Cimetidine	Inhibition of metabolisation of paroxetine, therefore potentially higher plasma levels with higher risk for side effects
Cisapride	Higher plasma levels of antidepressant with higher risk of side effects
Digitoxine	Potenial lower plasma levals of digitoxine with lower efficacy
Immunosuppressants	Higher plasma levels of immunosuppressants with fluvoxamine and fluoxetine
Theophyllin, Coffein	Inhibition of metabolisation of theophyllin with fluvoxamine, therefore higher risk of theophyllin side effects
Tramadole	Risk of central serotonine syndrome
Venalafaxine	
Beta-Blocker	Inhibition of metabolisation, therefore potentially higher plasma levels with higher risk for side effects
Carbamazepine	Risk of lower plasma level of venlafaxine because of induction of enzymes (CYP)
SSRI	Risk of higher plasma levels of venlafaxine because of slower metabolisation
Tramadole	Risk of central serotonine syndrome
MAO inhibitors	
Serotonergic drugs (especially SSRI)	Potentiation of effects and risk of central serotonergic syndrome
Sympathomimetic drugs (epinephrine and other catecholamines, ephedrine)	Risk of hypertensive crisis

patients with identified risks (e.g., low weight gain) are recommended.

Following childbirth, many women are at high risk for the onset or recurrence of a mood disorder. The transient 7–10-day depressive syndrome referred to as "postpartum blues" typically does not meet the criteria for major depressive disorder and does not require medication (APA 2000). The term "postpartum depression" refers to a major depressive episode occurring within 4 weeks of delivery. Studies have shown a consistent incidence of depression in 10–15% of mothers in the early weeks after delivery (Hoffbrand et al. 2001). Women with a history of MDD have a 25–50% risk of a postpartum depressive episode. Since many women needing antidepressant treatment may wish to breast-feed their infants, several recent studies have identified antidepressants that can be safely used during nursing (Wisner et al. 1996; Burt et al. 2001; Hoffbrand et al. 2001). The agents most scrutinized in breast-feeding women are paroxetine, sertraline, fluoxetine, clomipramine and nortriptyline (Stowe et al. 2000; Hendrick et al. 2001). Data from a pragmatic two-arm individually randomised controlled trial in general practice (RESPOND) show that at 4 weeks post-partum, women with a moderate postnatal depression randomized to an antidepressant, usually an SSRI, were twice as likely to have improved compared to listening visits started after 4 weeks post-partum of general supportive care (Sharp et al. 2010).

When a psychotropic medication is administered, the infant should be monitored daily by the mother for changes in sleep, feeding patterns and behaviour. The mother should alert the physician if there is any reason for concern.

Electroconvulsive therapy (ECT) should be considered as a first-line strategy for pregnant women especially during the first trimester.

5. Personalized treatment approaches

A systematic shortcoming of today's treatment recommendations is that they do not account for inter-individual differences in response patterns. Individualized (personalized) treatment approaches aim at selecting among different treatment options based on individual response predictors. Although (particularly for antidepressant treatments) there have been a wide array of genetic studies which have described possible response predictors, their results are still not fully transferable to clinical practice. In order to prescribe the right drug at the right dosage at the right time to the right patient, further variations added by gene regulation, including epigenetic mechanisms, as well as gene–environment interaction will have to be taken into account.

Particularly, in cases of non-response or partial response to an initial antidepressant monotherapy, selection of the next strategy is mainly based on evidence from large-scale studies from heterogeneous samples in terms of biological entities and response patterns. A predictor- and evidence-based navigation through treatment guidelines and algorithms will be of high clinical relevance and help avoiding treatment attempts which are not likely to be successful for a particular patient. This chapter presents some examples for promising outcomes in the field of predictor research which could serve for an individualized decision making, depending on replication and feasibility issues in clinical routine.

In terms of a predicting factor of specific antidepressive compounds, studies have mainly focused on candidate genes of the monoaminergic system (Binder and Holsboer 2006). In summary, single genetic variants in serotonin signalling have been shown to influence response to SSRI, genetic variants in norepinephrine signalling seem to influence response to NRI, and genetic variants in the glucocorticoid receptor gene are associated with response to various types of antidepressants (Uher et al. 2009). However, the effects are very modest and further modulated by epigenetic mechanisms and, hence, not suitable to guide the decision-making between different antidepressants (Uher 2011).

Lithium augmentation is associated with a response rate of 40–50% in patients who have not sufficiently responded to a previous treatment with an antidepressant. However, the search for clinical response predictors has not delivered any coherent results (Bschor et al. 2001). In the only study to date, the serotonin transporter polymorphism 5HTTLPR has been shown to be associated with response to lithium augmentation (Stamm et al. 2008). In this study, homozygous carriers of the short (s-) allele had a significantly higher likelihood to respond to this strategy than carriers of the long (l-) allele. As the short allele is also associated with poor response to SSRI, this subgroup might particularly benefit from an augmentation strategy. Another genetic polymorphism associated with response to lithium augmentation is the –50T/C SNP of the intracellular serin-threonin-kinase glycogen synthase kinase 3beta (GSK3B; Adli et al. 2007). Heterozygous and homozygous carriers of the C-allele have been shown to have a superior response to lithium augmentation in antidepressant non-responders. GSK3B is highly expressed in all cell tissues, particularly in the brain (Woodgett 1990). Lithium can directly and indirectly inhibit GSK3B, an effect which is generally anti-apoptotic and leads to the activation of cell survival-transcription factors (e.g., CREB) (Gould et al. 2004; Chin et al. 2005; Yin et al. 2006).

Interestingly, bipolar patients with a CC or CT genotype have previously found to respond better to lithium prophylaxis than homozygous TT carriers (Benedetti et al. 2005).

Genetic polymorphisms which lead to different levels of enzymatic activity are known for the cytochrome P450 isoenzymes 1A2, 3A4, 2C9, 2C19 and 2D6. For CYP 2D6, which metabolizes a wide variety of antidepressants differential dosing regimens have been recommended which may account for subsequent differences of metabolizing status (i.e. slow, normal, intermediate, ultra-rapid) (Kirchheiner et al. 2004). Roughly 10% of the Caucasian population are atypical metabolizers (slow or ultra-rapid) and require individual dose adaption depending on whether a compound can use parallel metabolizing pathways and whether the metabolite is an active compound itself. However, although recommended in non-responders with plasma levels outside the therapeutic range, CYP 2D6 genotyping is not used in routine clinical practice.

Genetic polymorphisms of FKBP5, a co-chaperone of hsp90 which regulates glucocorticoid receptor activity (particularly for rs 1360780) has been associated with *response* to antidepressants independent from drug class (Binder et al. 2004; Kirchheiner et al. 2008). Homozygous carriers of the (risk) allele show faster response to antidepressants (as well as more frequent depressive episodes) compared to persons with alternative genotypes that need about 10 days longer to show response.

P-glykoprotein (P-gp) acts as a transporter molecule at the *blood–brain barrier* where it functions as an active efflux pump that safeguards the brain from a variety of drugs and steroids and is encoded by the multidrug-resistance gene ABCB1. Genetic variants of this gene have been shown to account for differences in the response to antidepressants which are substrates of P-gp by directly influencing their penetration and thus bioavailability in the brain (Uhr et al. 2008). Among the substrates are amitriptyline, paroxetine, citalopram and venlafaxine (but not mirtazapine and fluoxetine).

We can expect that results from genome-wide assays will broaden our knowledge and foster the validity of our findings regarding genetic predictors. Successful integration of genetic predictors as well as further biomarkers and neuroimaging data into a combined model could open the door to an effective and clinically applicable personalized treatment of depression.

6. Novel pharmacological approaches

There exist new antidepressant approaches which may become part of the antidepressant armentarium in the near feature (e.g., NMDA receptor antagonists (ketamine) (Mathews et al. 2012) or multimodal serotonergic agents (e.g., LUAA21004, Adell 2010).

7. Update of Guidelines

The Guidelines will be updated in 2018 and will review recommendations in the light of new evidence from ongoing trials.

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