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REVIEW/MINI-REVIEW ▸

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Acute and Continuation Treatment of Major Depressive Disorder

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Summary

These practice guidelines for the biological treatment of unipolar depressive disorders were developed by an international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP). The goal for developing these guidelines was 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. These guidelines are intended for use by all physicians seeing and treating patients with these conditions. The data used for developing these guidelines have been extracted primarily from various national treatment guidelines and panels for depressive disorders, as well as from meta-analyses and reviews on the efficacy of antidepressant medications and other biological treatment interventions identified by a search of the MEDLINE database and Cochrane Library. The identified literature was evaluated with respect to the strength of evidence for its efficacy and was then categorized into four levels of evidence (A-D). This first part of the guidelines covers disease definition, classification, epidemiology and course of unipolar depressive disorders, as well as the management of the acute and continuation-phase treatment. These guidelines are primarily concerned with the biological treatment (including antidepressants, other psychopharmacological and hormonal medications, electroconvulsive therapy, light therapy, adjunctive and novel therapeutic strategies) of young adults and also, albeit to a lesser extent, children, adolescents and older adults.

Key words: *major depressive disorder, acute treatment, continuation treatment, evidence-based guidelines, biological treatment, pharmacotherapy, antidepressants.*

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• General Recommendations

Specific treatment is indicated for patients who meet diagnostic criteria for major depressive episode (DSM-IV) or moderate to severe depressive episode (ICD-10). Prior to treatment initiation, a comprehensive treatment plan should be developed and implemented based on the history and experience of previous treatments, current clinical subtype, current findings from examinations, severity of illness and risk of suicide. Other concurrent psychiatric and somatic disorders, non-psychiatric medications or psychosocial stress factors that might contribute to a depressive syndrome or interfere with treatment must be thoroughly considered. Independent of the choice of the specific treatment intervention, components of psychiatric management and general "psychotherapeutic support" 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 risk of suicide; reassessing the adequacy of diagnosis; monitoring the patient's treatment response, side effects and general medical condition; and enhancing treatment adherence by providing education to patients and families. The ultimate goal of the acute treatment phase is to achieve remission. Growing evidence indicates that acute-phase medication trials at adequate doses should last at least six weeks, and eight to 10 weeks to define the full extent of symptom reduction. The degree of benefit from adequate treatment appears to increase with severity of depression. The goal of the continuation treatment phase is to prevent an early relapse, to eliminate any residual symptoms and to restore patients to their prior level of psychosocial and occupational functioning. Successful treatment of depressed patients with antidepressants includes the education of the patients and their families regarding available treatment options, the time it takes to see a response, early side effects and what to do about them, and the expected course of treatment.

• Specific Treatment Recommendations

Antidepressants are the first-line treatment for major depressive episodes (moderate to severe depressive episode). Choosing an antidepressant depends on various factors that should be considered: prior experience with medication (response, tolerability, adverse effects), concurrent medical conditions and concomitant use of nonpsychiatric medications, a drug's short- and long-term side effects, atypical features of the depressive episode, clinical subtype of depression, physician's experience with the medication, patient's history of adherence to medication, history of first-degree relatives responding to a medication, patient preferences, and the cost and availability of specific antidepressants. There is no decisive evidence that any class of antidepressants is more efficacious or has a more rapid onset than another, although there may be slight differences for clinical subtypes. There is evidence that some tricyclic antidepressants (TCAs) (amitryptiline and clomipramine), and venlafaxine are more effective than SSRIs in severely depressed, hospitalized patients. Depressed patients with atypical features particularly benefit from the irreversible monoamine oxidase inhibitors (MAOIs). Antidepressants differ in their side effect profile, potential to interact with other drugs and safety in overdose. Second and third generation ("newer") antidepressants (e.g., SSRIs, mirtazapine, nefadozone, reboxetine and venlafaxine) are generally better tolerated than the first generation ("older") TCAs and tetracyclic antidepressants, and are less likely to be discontinued. Regardless of the initial choice of antidepressant, about 30% to 50% of depressions will not respond sufficiently to adequately performed first-line treatment. A review of the diagnosis, adequacy of initial treatment and underlying psychosocial stress factors is then recommended. Various treatment strategies have been proposed for depressions not responding or only partially responding to an adequately performed first trial with an antidepressant. The major types of strategies employed are: (1) switching to a new antidepressant from a different pharmacological class; (2) switching to a new antidepressant within the same pharmacological class; (3) combining two antidepressants from different classes; (4) augmenting the antidepressant with other agents (e.g., lithium, thyroid hormone, pindolol, oestrogen, buspirone) to enhance antidepressant efficacy; and (5) combining the antidepressant with a psychotherapeutic intervention. Among these strategies, augmentation with lithium is the foremost and most well-documented strategy. Electroconvulsive therapy (ECT) should be considered as a first-line strategy in special situations when rapid relief from depression is required (e.g., severe psychotic depression, severe depression with psychomotor retardation, "true" or "absolute" treatment-resistant depression, continued refusal of food intake, severe suicidality), and in patients who have experienced a previous positive response to ECT.

1 Unipolar depressive disorders

1.1 Introduction

Unipolar depressive disorders are characterized by depressive symptoms only, without any history of a manic, mixed or hypomanic episode. This criterion distinguishes them from the group of bipolar (affective) disorders. Among the unipolar depressive disorders, three main diagnostic groups can be distinguished (DSM-IV, American Psychiatric Association 1994) (the corresponding ICD-10 diagnoses are given

in parentheses; World Health Organization 1992):

- major depressive disorder (MDD) - single episode or recurrent (ICD-10: depressive episode or recurrent depressive disorder),
- dysthymic disorder (ICD-10: dysthymia) and other chronic depressive disorders (MDD in incomplete remission and chronic MDD), and
- "subthreshold depressions" (depressive disorder not otherwise specified (NOS) including minor depressive disorder (MinD), recurrent brief depressive disorder (RBD) and subsyndromal symptomatic depression (SSD) (ICD-10: depressive episode, unspecified, unspecified mood disorder and other mood disorders, recurrent brief depressive disorder).

Major depressive disorder (MDD) is the most studied among the unipolar depressive disorders. Thus, the recommendations included in these guidelines will focus on the acute, continuation (Part 1) and maintenance (Part 2) treatment of major depressive disorder. Recommendations for the treatment of other chronic depressive disorders and subthreshold depressions will also be given in Part 2 of these guidelines (Bauer et al In Press).

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 arrived at by consensus with the WFSBP Task Force on Unipolar Depressive Disorders consisting of 46 international researchers and clinicians. The goal for developing these guidelines was to systematically review all available evidence pertaining to the treatment of unipolar depressive disorders, and to produce a series of recommendations that are clinically and scientifically meaningful. They were also intended to bring together the various opinions of scientifically respected experts and international representatives on the appropriate state-of-the-art treatment of these disorders. There were a few aspects for which it was not possible to reach a consensus within the Task Force. In such cases, the Chairman and Co-Chairmen had to make a final decision. The most divergent opinions were in the following areas: the classification of antidepressants, the positioning and efficacy of the herbal remedy St. John's wort (e.g., is it an antidepressant at all ?), the use and efficacy of benzodiazepines as an adjunctive treatment for depressive disorders, the use of neuroleptics for the treatment of non-psychotic depressive disorders, and the positioning of psychotherapy in guidelines for the biological treatment of depressive disorders.

These guidelines are intended for use in clincal practice by *all* physicians seeing and treating patients with these conditions. They should be considered as guidelines only because the ultimate judgment regarding a particular treatment procedure 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 are primarily concerned with the biological (somatic) treatment (e.g., antidepressants, other psychopharmacological and hormonal medications, electroconvulsive therapy, light therapy) of young adults, but also, albeit to a lesser extent, of children, adolescents and older adults. They do not address depressive disorders occurring in bipolar affective disorders (which will be covered by separate WFSBP guidelines). Psychotherapeutic treatment interventions are covered only briefly, but references are provided for further reading. Since the availability of medications, treatments and diagnostic procedures varies considerably across countries, the authors have included several different treatment options in the guidelines.

1.3 Methods of literature research and data extraction

The data used for the development of these guidelines have been extracted from the following sources: Agency for Health Care Policy and Research (AHCPR) Depression Guidelines Panel (AHCPR 1993); AHCPR Evidence Report on Treatment of Depression: Newer Pharmacotherapies (AHCPR 1999); American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Revision (American Psychiatric Association 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, CANMAT, Clinical Guidelines for the Treatment of Depressive Disorders (CANMAT 2000); Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder (Lam and Levitt 1999); Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde, DGPPN, Praxisleitlinien in Psychiatrie und Psychotherapie, Affektive Erkrankungen (DGPPN 2000); American Academy of Child and Adolescent Psychiatry, Practice Parameters for the Assessment and Treatment of Children and Adolscents with Depressive Disorders (American Academy of Child and Adolescent Psychiatry 1998); The Cochrane Library; meta-analyses on the efficacy of antidepressant medications identified by a search in the MEDLINE database (until August 2001); major pertinent review articles identified by a search in the MEDLINE database and textbooks, and individual clinical experience by the authors and members of the WFSBP Task Force on Unipolar Depressive Disorders. With respect to quoting original data, only research articles published in peer-reviewed journals in English before August 2001 were considered.

1.4 Evidence-based classification of recommendations

The evidence found in the literature research and data extraction was summarized and categorized to reflect its susceptibility to bias (Shekelle et al 1999). Each treatment recommendation was evaluated with respect to the strength of evidence for its efficacy, safety and feasibility[1]. However, daily treatment costs were not taken into consideration due to the variability of medication costs worldwide. Four categories of evidence were used:

Level A: Good research-based evidence to support the recommendation. This level is achieved if research-based evidence for efficacy is given from at least three moderately large, positive, randomized controlled (double-blind) studies (RCT). In addition, at least one of these three studies must be a well-conducted, placebo-controlled study.

Level B: Fair research-based evidence to support the recommendation. This includes evidence of efficacy from at least two moderately large randomized, double-blind studies (this can be either ≥ two comparator studies or one comparator-controlled and one placebo-controlled study) or from one moderately large randomized, double-blind study (placebo-controlled or comparator-controlled) and ≥ one prospective, moderately large (sample size of ≥ 50 participants), open-label, naturalistic study.

Level C: Minimal research-based evidence to support the recommendation. This level is achieved if one randomized, double-blind study with a comparator treatment and one prospective, open-label study/case series (with a sample size of ≥ 10 participants) showed efficacy, or at least two prospective, open-label study/case series (with a sample size of ≥ 10 participants) showed efficacy.

Level D: Expert opinion-based (from authors and members of the WFSBP Task Force on Unipolar Depression) supported by at least one prospective, open-label study / case series (sample size ≥ 10 participants).

No level of evidence: Expert opinion for general treatment procedures and principles.

1.5 Epidemiology and course of major depressive disorder

Major depressive disorder (MDD) is a severe mood disorder, associated with significant morbidity and mortality, that affects individuals of all ages and races. The recent worldwide Global Burden of Disease (GBD) study by the World Health Organization (WHO) has shown variations by country and region, but patterns and trends regarding depressive disorders are remarkably similar worldwide (Murray and Lopez 1997a,b). MDD is characterized by single or recurrent major depressive episodes (MDEs). The essential feature of a major depressive episode is a period of at least two weeks of depressed mood with abnormalities of neurovegetative functions (appetite, weight loss, sleep disturbances), psychomotor 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 1). MDD has a median lifetime prevalence of 16.1% (range 4.4-18) (Wittchen 2000). It occurs in about 5% to 10% of the adult population during any one-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). A review of epidemiological studies performed in various countries and continents indicated that the median of the point prevalence for major depressive disorder in adults age 18-65 is 3.1 (range 1.7% to 3.7%) (Wittchen 2000).

The age of onset of MDD is difficult to assess because the first episode is frequently mild and untreated, and sometimes recognized many years later in retrospect. MDD can begin at any age, even in childhood and adolescence (Chapter 4.2), but there are two peaks in the twenties and forties (Angst and Preisig 1995; American Psychiatric Association 2000). A mean age of onset of MDD has been estimated around the age of 30 (Wittchen 2000).

Female gender, a previous episode of major depression and a positive first-degree family history of depression are the most consistently described risk factors for a depressive illness. Family and twin studies have indicated that MDD is a complex genetic disorder being 1.5-3 times more common among first-degree biological relatives of persons with this disorder than among the general population (Maier et al 2000; Sullivan et al 2000).

An untreated depressive episode typically lasts about six months or longer (Angst and Preisig 1995; Solomon et al 1997; American Psychiatric Association 2000). Modern pharmacotherapy alleviates suffering during acute episodes of the condition, and placebo-controlled trials show response and remission occurring more quickly in actively treated groups. A 27-year prospective study of 186 unipolar depressed patients meeting DSM-III criteria for major depression found a decreasing episode (cycle) with increasing episode number (Angst and Preisig 1995). However, a 10-year prospective study of 258 subjects treated for unipolar major depressive disorder showed that the duration of recurrent mood episodes remained relatively uniform over time and averaged approximately 20 weeks (Solomon et al 1997). MDD is a recurrent disorder and 50%

1 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. Levels of recommendation only apply to treatment and not to other aspects.

Table 1
Classification and criteria of major depressive disorder (DSM-IV) and depressive episode (ICD-10)

DSM-IV[a] (code)	ICD-10[b] (code)
Major depressive disorder A. single episode (296.2x) B. recurrent (296.3x)	A. Depressive episode • mild (F32.0): at least 2 typical symptoms, plus at least 2 other common symptoms; none of the 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
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).	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.

[a] 4th Revision of the American Psychiatric Association's Diagnostic and Statistics Manual (American Psychiatric Association 1994)
[b] 10th Revision of the International Classification of Diseases (World Health Organization 1992)

to 85% of the patients who have an episode will eventually have another episode (Keller et al 1986; Mueller et al 1999). There is also increasing evidence that some who experience a major depressive episode will have a lifelong course of illness either through recurrent major depressive episodes or other forms of chronic depressive disorders, e.g. recurrent MDD without full inter-episodic recovery, or currently in a chronic major depressive episode, or "double depression" (concurrent major depression and dysthymic disorder) (for more information on chronic depressive disorders, see Part 2 of these guidelines (Bauer et al In Press)) (Brunello et al 1995; Angst 1999a; Judd et al 1998; Judd et al 2000b). Between 9% and 24% of patients with the initial diagnosis of a major depressive episode will undergo a change in diagnosis over time, mostly to bipolar disorder (Angst and Preisig 1995; Solomon et al 1997).

Although the prognosis for a depressive episode is good, with most patients returning to normal functioning when an episode is over, in 20% to 30% of cases, instead of complete remission, some depressive symptoms persist chronically (Keller et al 1986; Angst 1986; Scott 1988; Paykel 1994; Judd et al 1998; see also Part 2 of these guidelines (Bauer et al In Press)). 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 2000a; Hirschfeld et al 2000). Studies investigating the effects of depression on health-related quality of life demonstrate decrements that equal or exceed those of patients with chronic medical illnesses such as ischaemic heart disease or diabetes mellitus (Wells et al 1989b; AHCPR 1999; Unützer et al 2000a).

The most serious consequence of MDD is suicide. It has been estimated that about 50% of depressed patients make at least one suicide

attempt during their lifetime. It is well established that patients with affective disorders suffer a higher risk of suicide relative to the general population (Angst 1999b). However, no risk factor or classification of diagnostic subtype has been shown to reliably predict suicide (Bostwick and Pankratz 2000). In a recent meta-analysis, the lifetime prevalence of suicide was estimated based on the intensity of the treatment setting. The analysis showed that clinically depressed patients who have been hospitalized for suicidality have a lifetime risk of suicide of 8.6%. Patients with affective disorders, who have been hospitalized without specification of suicidality, have a lifetime suicide rate of 4.0%. The lifetime suicide prevalence for mixed inpatient/outpatient populations was 2.2%, and less than 0.5% for the nonaffectively ill population (Bostwick and Pankratz 2000). Depression also substantially increases the risk of death by cardiovascular disease (Wulsin et al 1999).

The recent 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, the burden of unipolar major depression increased by nearly 40% (Murray and Lopez 1997a). By the year 2020, unipolar MDD is projected to be the second largest contributor to the global burden of disease, after heart disease (Murray and Lopez 1997b).

In addition to the personal suffering of individuals and their families, depression imposes significant costs on society (Brunello et al 1995). Because depression is often not properly diagnosed and often undertreated (Wells et al 1989a; Üstün and Sartorius 1995; Unützer et al 2000b; Young et al 2001), and because it begins to affect many people at a relatively early age, it causes costs over a longer period of time. It is important to measure the economic cost of illness, which includes both the direct total health care costs and indirect costs (the latter have been estimated to be much higher than the direct costs). Direct costs include mental health treatment costs and all other health care costs. Indirect costs include such varied factors as lost productivity associated with the morbidity and mortality of depression (Booth et al 1997). It has been estimated that the annual cost of depression totals approximately $43.7 billion in the United States (Greenberg et al 1993).

1.6 Indications and goals of treatment for major depressive disorder

Specific antidepressant treatment is indicated for patients who meet diagnostic criteria for a major depressive episode (DSM-IV) or a moderate to severe depressive episode (ICD-10) (for criteria and discrepancies between these two classification systems, see Table 1). Current diagnostic criteria in both classification systems represent a clinical and historical consensus about the most prominent and important symptoms and signs of depressive illness. 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") conditions to more event-dependent (formerly "reactive") conditions (Table 2). However, it has not been found generally useful to distinguish between these different types when making treatment recommendations (Anderson et al 2000).

Table 2
Traditional clinical classification of depressive disorders and corresponding codes in ICD-9[a] and ICD-10[b]

Traditional Clinical Classification	ICD-10 Classification	ICD-10 code	ICD-9 code
Endogenous depression, unipolar	Depressive episode[c]	F 32	296.1
	Recurrent depressive disorder[c]	F 33	296.1
Endogenous depression, bipolar	Bipolar affective disorder, current episode depression	F 31	296.3
Neurotic depression	Dysthymia	F 34.1	300.4
Adjustment reaction	Adjustment disorders	F 43.2	309
Brief depressive reaction	Brief depressive reaction	F 43.22	309.0
Prolonged depressive reaction	Prolonged depressive reaction	F 43.21	309.1
Organic depression in physical condition	Organic depressive disorder	F 06.32	294.8
Senile dementia with depressive features	Dementia, predominantly depressive symptoms	F 03.x3	290.2

[a] 9th Revision of the International Classification of Diseases (World Health Organization 1978)
[b] 10th Revision of the International Classification of Diseases (World Health Organization 1992)
[c] current severity of episode: mild (F 32.0, F 33.0), moderate (F 32.1, F 33.1), severe (F 32.2, F 33.2)

Prior to treatment initiation, 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.

There are acute, intermediate and long-term goals for the treatment of major depressive disorder. The ultimate goal of the acute treatment phase is to achieve remission. There is a consensus that the criteria for remission should involve at least two things: the patient should be asymptomatic (not meet the criteria for diagnosis of the disorder and have minimal residual symptoms), and have an improvement in psychosocial and occupational functioning. The intermediate goal is to prevent a relapse, to eliminate any residual symptoms and to restore patients to their prior level of functioning. The long-term goal is to prevent future episodes (prophylaxis) (AHCPR 1993; American Psychiatric Association 2000; Bauer and Helmchen 2000).

The typical course of a major depressive episode, including the risk of recurrence and its corresponding structured treatment approach, is represented in a model developed by Kupfer and colleagues (Kupfer 1993). In this model, the three phases of treatment correspond to three stages of the illness: (1) acute therapy, (2) continuation therapy, and (3) maintenance therapy. The *acute phase* of therapy covers the time period from the initiation of treatment to remission, which is the primary therapeutic goal (usually achieved at a score of ≤ 7 on the 17-item Hamilton Rating Scale for Depression) (Frank et al 1991; Kupfer 1993). The term "treatment response" describes a state of improvement in the patient's condition of sufficient quality to result in the treating physician's impression of at least a moderate degree of global improvement and a ≥ 50% reduction in depressive symptomatology (Thase 1990). If the premorbid level of functioning is fully reestablished by acute therapy, it is considered a remission (for definitions of the terms related to treatment response see Chapter 2.1.4) (Kupfer 1993). 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, a relapse has occurred. When the patient has been asymptomatic for approximately six months, a recovery from the episode has occurred. The recovery may be confirmed by continued absence of depressive symptoms after the cessation of medication. Recovery applies only to individual episodes of the illness and does not imply that the patient would be free of recurrences if prophylactic therapy was discontinued (Bauer and Helmchen 2000). Long-term *maintenance treatment* is aimed at the prevention of a new episode of depression. Guidelines for the maintenance treatment of unipolar major depressive disorder will be given in Part 2 of these guidelines (Bauer et al In Press).

2 Acute-phase treatment of major depressive disorder

These guidelines begin at the point where 1) the diagnosis of a major depressive episode has been made by a physician according to one of the two established classification systems, the International Classification of Diseases (ICD-10; World Health Organization 1992) or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association 1994), 2) other 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), and 3) other factors (e.g., non-psychiatric medications or psychosocial stress factors) that might contribute to a depressive syndrome or interfere with treatment have been thoroughly considered. It should be emphasized that the initial assessment of depression, including a thorough somatic examination, is a physician's task.

The most common treatments for major depressive disorder will be reviewed in the following, with a focus on somatic treatment interventions. Several medications are available to be used alone or in combination. Independent of the choice of the specific treatment intervention, components of psychiatric management and general "psychotherapeutic support" (Thase and Howland 1994; American Psychiatric Association 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 of suicide); reassessing the adequacy of diagnosis; monitoring the patient's treatment response, side effects and general medical condition, and enhancing treatment adherence by providing education to patients and families (American Psychiatric Association 2000). During the acute treatment phase, weekly or bi-weekly visits are recommended. During the continuation phase, the frequency of visits may vary, but a frequency of one visit every one to two months is recommended.

2.1 Antidepressants

One of the most important achievements in the treatment of major depression was the development of antidepressant medications. Since the introduction of the first tricyclic anti-

Table 3
Antidepressants: Mode of action and commonly used doses

Generic Name[a] (in alphabetical order)	Traditional Structural Classification	Functional Classification/ Primary Pharmacological Action[b]	Starting Dose[c] (mg/day)	Standard Dose[d] (mg/day)	Plasma Levels[e] (Therapeutic range) (ng/mL)
Amineptine		DRI	100	200-300	
Amitriptyline[f]	TCA	NRI>SRI	25-50	100-300	80-200
Amoxapine	TetraCA	NRI>SRI	50	100-400	
Bupropion[g]		DRI	150	150-450	
Citalopram		SRI	20	20-40 (60)	
Clomipramine[h]	TCA	SRI>NRI	25-50	100-250	175-300
Desipramine	TCA	NRI	25-50	100-300	100-300
Dibenzepine	TCA	NRI>SRI	120-180	240-720	
Doslepine	TCA	NRI>SRI	75	75-150	
Dothiepin	TCA	NRI>SRI	25-50	100-300	
Doxepine	TCA	NRI>SRI	25-50	100-300	
Fluoxetine		SRI	20	20-40 (60)	
Fluvoxamine		SRI	50	100-250	
Imipramine	TCA	NRI>SRI	25-50	100-300	175-300
Isocarboxazid[i]	MAO-I	20	20-60		
Lofepramine	TCA	NRI	70	140-210	
Maprotiline	TetraCA	NRI	25-50	150-225	
Mianserin		5-HT_2, $\alpha_1 + \alpha_2$	30	60-120	
Milnacipran		SRI+NRI	50-100	100-200	
Mirtazapine		5-HT_2 + 5-HT_3, $\alpha_2 > \alpha_1$	15	15-45	
Moclobemide		RIMA (MAO-A)	150	300-600	
Nefazodone		5-HT_2 > SRI	100	300-600	
Nortriptyline	TCA	NRI	25-50	75-200	70-170
Paroxetine		SRI	20	20-40 (60)	
Phenelzine[i]		MAO-I	15	30-90	
Protriptyline	TCA	NRI>SRI	10	20-60	
Reboxetine		NRI	4-8	8-12	
Sertraline		SRI	50	50-200	
Setiptiline	TetraCA	5-HT_2, $\alpha_1 + \alpha_2$	3	3-6	
Tianeptine	TCA	SRS	12.5	25-37.5	
Tranylcypromine[i]		MAO-I	10	20-60	
Trazodone		5-HT_2, α_1 > SRI	50-100	200-600	
Trimipramine	TCA	NRI>SRI	25-50	100-300	
Venlafaxine[j]		SRI+NRI	37.5-75	75-375	200-450
Viloxazine		NRI	100	200-500	

[a] availability on the markets differs considerably across countries;
[b] see abbreviations; extracted from: Richelson 1994, Bezchlibnyk-Butler and Jeffries 1996, Anderson et al. 2000, Kent 2000, Richelson 2001;
[c] lower starting doses may be needed for older adults (>60) or patients with comorbid medical illness (especially cardiovascular conditions; see text);
[d] standard doses are generally lower in Japan;
[e] only given for those antidepressants with well established therapeutic range (Perry et al. 1994);
Indications other than depression (approved in some countries) or common uses:
[f] chronic pain;
[g] smoking cessation;
[h] obsessive-compulsive disorder (OCD);
[i] anxiety disorders (panic disorders, PTSD, social phobia);
[j] generalized anxiety disorder.

Abbreviations:
$\alpha_1 = \alpha_1$ receptor antagonism
$\alpha_2 = \alpha_2$ receptor antagonism
DRI = dopamine reuptake inhibition
5-HT_2 = 5-HT_2 receptor antagonism
5-HT_3 = 5-HT_3 receptor antagonism
MAO-I = irreversible inhibition of monoamine oxidase (MAO)
NRI = noradrenaline reuptake inhibition
SRI = serotonin (5-HT) reuptake inhibition
SRS = serotonin reuptake stimulation
RIMA = reversible inhibition of monoamine oxidase A (MAO-A)
TCA = tricyclic antidepressant
TetraCA = tetracyclic antidepressant

depressant (TCA), imipramine, in 1957, many different types of antidepressants have been introduced to the pharmacotherapeutic armamentarium. There are currently at least 35 different antidepressants available worldwide, however, the availability on the markets in individual countries varies considerably (Table 3).

The "newer" antidepressants were developed to act specifically on the serotonergic and noradrenergic systems, but with fewer side effects, a more rapid onset, and less toxicity than the

TCAs (Leonard 1995; Feighner 1999; Montgomery 1999; Möller 2000). However, the classes of antidepressants currently available differ little in their antidepressant efficacy. There is no decisive evidence that any class of antidepressants is more efficacious or has a more rapid onset than another, although there may be differences for particular types of depression (see below) (AHCPR 1993; Potter and Schmidt 1997; AHCPR 1999; American Psychiatric Association 2000; Anderson 2001). There is also no clear difference in efficacy between individual antidepressant medications. All current available antidepressants produce treatment responses of 50% to 75% in moderately to severely depressed patients.

Thus, the selection of a particular antidepressant for the individual patient depends on various factors that should be taken into consideration (adapted from AHCPR 1993): prior experience with medication (positive/negative response), concurrent medical conditions that may be worsened by selected antidepressants, concomitant use of nonpsychiatric medications that may lead to negative drug-drug interactions, a drug's short- and long-term side effects (those side effects which affect quality of life are critical for patients' satisfaction and compliance), atypical features of the depressive episode, type of depression, physician's experience with the medication, patient's history of adherence to medication, history of first-degree relatives responding to a medication, patient preferences, and the cost and availability of specific antidepressants. It should be emphasized that certain individuals may show consistent response to one class of antidepressants, even if this is not particularly reflected in the clinical subtype.

Successful treatment of depressed patients with antidepressants includes the education of the patients and their families regarding available treatment options, the time it takes to see a response, early side effects and what to do about them, and the expected course of treatment. To reduce early side effects that might interfere with medication adherence, a slow start with medication is particularly wise for TCAs (see Table 3). Difficulties and barriers to medication adherence should be proactively anticipated and addressed at each contact with the patient. Short-term and long-term side effects are major contributors to treatment discontinuation.

2.1.1 *Classification and efficacy*

Unfortunately, classifications of antidepressants used in clinical practice are mostly based on historical factors, as well as structural and pharmacological properties, but do not always follow a systematic approach. Traditionally, antidepressant medications were grouped into the following main categories: tricyclic antidepressants, tetracyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOI) (including irreversible MAOIs and reversible inhibitors of monoamine oxidase A [RIMA]), and "other" antidepressants (including serotonin-norepinephrine reuptake inhibitors [SNRIs], 5-HT_2 receptor antagonists, norepinephrine reuptake inhibitors [NRIs], dopamine-norepinephrine reuptake inhibitors). These categories are used in these guidelines, however, due to this unsystematic classification, antidepressants are listed in Table 3 in alphabetical order.

Efficacy in treating major depressive disorder has been well established in numerous placebo-controlled studies for the "older" antidepressants, including the tricyclics, tetracyclics and irreversible MAO inhibitors (all classes Level A) (Khan et al 2000; Storosum et al 2001). It has been estimated from double-blind trials that 50% to 75% of patients with severe to moderate severe major depression respond to tri- and tetracyclic antidepressants compared to 25% to 33% treated with placebo (American Psychiatric Association 2000). However, the magnitude of the effect is rather modest compared with placebo in milder forms of major depression, particularly in primary care studies (Level A) (Paykel et al 1988; Anderson et al 2000).

Similarly, numerous double-blind controlled trials have demonstrated superior efficacy of the SSRIs compared to placebo (Level A) (Bech et al 2000; Khan et al 2000; Mace and Taylor 2000). A recent comprehensive report by the Agency for Health Care Policy and Research (AHCPR 1999) indicated that the "newer" antidepressants (defined as those released into the markets since 1980, including the SSRIs) are effective treatments for major depression and that they have similar efficacy compared to the "older" antidepressants (those released into the markets before 1980, including the tricyclic and tetracyclics antidepressants, and the irreversible MAO inhibitors). Numerous trials proved the "newer" antidepressants more efficacious than placebo with response rates of 50% for active treatment compared with 32% for placebo (Level A) (AHCPR 1999).

Although their efficacy is comparable to tricyclic antidepressants, the "older" (irreversible) MAO inhibitors (including tranylcypromine and phenelzine) are usually not considered first-line treatments because of the risk of a potentially fatal hypertensive crisis or serotonin syndrome (see below) in patients who eat tyramine-containing foods (e.g., aged cheese, aged or cured meats, soy sauce and soy bean condiments, salted fish and red wine) or use certain medications (American Psychiatric Association 2000).

2.1.2 *Comparative efficacy and tolerability*

The numerous tricyclics are equal in efficacy but

Table 4
Side effect profiles of antidepressants[a]

Generic Name (in alphabetical order)	Anti-cholinergic[b]	Nausea/ gastro intestinal	Sedation	Insomnia/agitation	Sexual dysfunction	Orthostatic hypotension	Weight gain	Specific adverse effects	Lethality in overdose
Amineptine	-	+	-	++	+	+	+	Risk of abuse (amphetamine-like effects)	Low
Amitriptyline	+++	-	+++	-	+	+++	+++	ECG changes[c]; may lower seizure threshold	High
Amoxapine	+++	-	+	++	+	+	+		High
Bupropion	+	+	-	+	-	-	-		Low
Citalopram	-	++	-	++	++	-	-		Low
Clomipramine	+++	+	+	+	++	++	++	ECG changes[c]; may lower seizure threshold	Moderate
Desipramine	+	-	-	++	+	+	+	ECG changes[c]; may lower seizure threshold	High
Dibenzepine	+	-	+	-	+	+	+	ECG changes[c]; may lower seizure threshold	Moderate
Doslepine	++	-	++	-	+	+	+	ECG changes[c]; may lower seizure threshold	High
Dothiepin	+++	-	+++	-	+	+++	+++	ECG changes[c]; may lower seizure threshold	High
Doxepine	+++	-	+++	-	++	+++	++	ECG changes[c]; may lower seizure threshold	High
Fluoxetine	-	++	-	++	++	-	-	Inhibitory effects on CYP2D6[d]	Low
Fluvoxamine	-	++	+	++	++	-	-	Inhibitory effects on CYP1A2, CYP2C19[d]	Low
Imipramine	++	-	+	++	+	++	++	ECG changes[c]; may lower seizure threshold	High
Isocarboxazid	+	+	-	++	+	++	+	Hypertensive crisis[e]; risk of serotonin syndrome[f]	High
Lofepramine	+	-	+	++	+	+	+	ECG changes[c]; 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[d]	Low
Nortriptyline	+	-	+	+	+	+	+	ECG changes[c]; may lower seizure threshold	High
Paroxetine	+	++	-	++	++	-	-	Inhibitory effects on CYP2D6[d]	Low
Phenelzine	+	+	+	++	++	++	+	Hypertensive crisis[e]; risk of serotonin syndrome[f]	High
Protriptyline	+++	-	+	++	+	++	+	ECG changes[c]; may lower seizure threshold	High
Reboxetine	-	+	-	++	+	++	-		Low
Sertraline	-	++	-	++	++	-	-		Low
Setiptiline	+	-	++	-	+	+	+		Moderate
Tianeptine	+	+	-	+	-	-	-	ECG changes[c]; may lower seizure threshold	Low
Tranylcypromine	+	+	+	++	+	++	+	Hypertensive crisis[e]; risk of serotonin syndrome[f]	High
Trazodone	-	+	++	-	++	+	+	Priapism (rare)	Low
Trimipramine	++	-	+++	-	+	++	++	ECG changes[c]; may lower seizure threshold	High
Venlafaxine	-	++	-	++	++	-	-	Hypertension	Low
Viloxazine	-	+	-	++	-	-	-		Low

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

[a] 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., Bezchlibnyk-Butler and Jeffries 1996, Benkert and Hippius 2000, Kent 2000), the primary literature or the complete prescribing information available in the package insert of the drug

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

[c] conduct delays

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

[e] increased risk with high tyramine containing food and sympathomimetic drugs

[f] in combination with serotonergic drugs.

differ in their side effect profile, with an advantage for the second over the first generation tricyclics (Level A) (Table 4) (Hotopf et al 1997). With respect to SSRIs, the group of antidepressants currently most widely prescribed around the world, a recent meta-analysis of 20 comparative acute treatment studies of the five currently available SSRIs (Tables 3 and 4) showed no significant difference in efficacy between individual compounds (Level A) (Edwards and Anderson 1999). Although robust differences in tolerability, side effects and theoretical risk of drug-drug interactions are lacking, subtle differences exist and may be important in selecting the appropriate SSRI compound for the individual patient (Edwards and Anderson 1999; Peretti et al 2000; Stahl 2000). For outpatients, meta-analyses revealed comparable overall effi-

cacy of the "older", irreversible MAO inhibitors (phenelzine, isocarboxazid and tranylcypromine) (Level A) (Thase et al 1995; American Psychiatric Association 2000). In one meta-analysis, the "newer", reversible, selective MAO-A inhibitor, moclobemide, was found to be slightly less effective, but better tolerated than "older" MAOIs (Level B) (Lotufo-Neto et al 1999). Moclobemide has shown equal efficacy compared with imipramine in a placebo-controlled trial (Versiani et al 1989).

In general, there are no clinically significant differences in efficacy and effectiveness between tricyclic antidepressants and SSRIs (Level A) (Möller et al 1994; Anderson 2000; American Psychiatric Association 2000; Bech et al 2000; Geddes et al 2001). There is evidence from a meta-analysis including 102 RCTs that TCAs may be more effective than SSRIs in hospitalized patients (who frequently present with melancholic features) and in severely ill patients (Level A) (Anderson 2000; American Psychiatric Association 2000). However, another meta-analysis of fewer RCTs using a different methodology found that the advantage of TCAs over SSRIs did not reach statistical significance (Geddes et al 2001). Another recent meta-analysis of 186 RCTs revealed that amitriptyline is less well tolerated than tricyclics/tetracyclics and SSRIs, although slightly more patients treated with amitriptyline recovered than those treated with an alternative antidepressant (Barbui and Hotopf 2001). In contrast, SSRIs are generally better tolerated that TCAs and show lower rates of treatment discontinuations overall (Level A) (Simon et al 1996; AHCPR 1999; Anderson 2000; Bech et al 2000; Peretti et al 2000). SSRIs are safer and have higher tolerability profiles compared with tricyclic and tetracyclic antidepressants by producing fewer anticholinergic side effects and cardiovascular toxicities (Level A) (Mace and Taylor 2000; Peretti et al 2000). Thus, SSRIs and other "newer antidepressants" are first-choice medications for mild to moderately severe depression, particularly in the outpatient and primary care setting, and in patients with cardiovascular diseases (Kasper 1997; Shores et al 1998).

With respect to the comparative efficacy among the "newer" antidepressants, recent meta-analyses have suggested superior efficacy of venlafaxine compared to SSRIs (Einarson et al 1999; Thase et al 2001; Anderson 2001).

Side effects vary between classes and to some extent between individual agents (Table 4). Concurrent nonpsychiatric medical conditions favour some agents over others because of their side effect profile, e.g., for patients with coronary artery disease, drugs that do not lower blood pressure or are associated with no cardiac conduction changes (e.g., bupropion, SSRIs, mianserin). Among the tricyclics, the secondary amines (e.g., desipramine, nortriptyline) have fewer side effects compared to the tertiary amines (e.g., amitriptyline, imipramine). If tricyclics are selected for the elderly, the seconday amines are preferred due to their lower rate of anticholinergic side effects. The most frequent side effects of TCAs and tetracyclics are: anticholinergic/ antimuscarinergic (dry mouth, constipation, blurred vision, urinary hesitation 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) (Table 4). Therefore, TCAs and tetracyclics should not be used in patients with moderate to severe cardiovascular disorders (Shores et al 1998), narrow-angle glaucoma, prostatic hypertrophy, cognitive impairment, seizures and delirium.

The most frequent side effects of SSRIs are: gastrointestinal (nausea, vomiting and diarrhoea), 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) (Table 4). SSRIs should be used with some caution in patients where these symptoms preexist and might be exacerbated with treatment. Contraindicated is the use of SSRIs in combination or shortly before/after treatment with MAO inhibitors because of the risk of serotonin syndrome. The serotonin syndrome is most commonly the result of the interaction between irreversible MAO inhibitors and SSRIs but can also occur with other serotonergic agents (e.g., clomipramine, L-tryptophan, fenfluramine, buspirone, venlafaxine, milnacipran, nefadozone and trazodone). The most frequent clinical features of the serotonin syndrome are changes in mental status, restlessness, myoclonus, hyperreflexia, shivering, abdomial pain, diarrhea and tremor (Sternbach 1995). Antidepressants with the lowest risk of sexual dysfunction are (in alphabetical order): amineptine, bupropion, mirtazapine, moclobemide and nefadozone (Ferguson 2001; Montejo et al 2001; for guidelines of managing antidepressant sexual side effects see Zajecka 2001). For more information on the most frequent side effects of the other/newer antidepressants, see Table 4.

An analysis of 206 randomized controlled trials evaluating the tolerability of the "newer" antidepressants versus the "older" antidepressants for depression (mostly major depression) indicated the following differences between the "newer" medications and TCAs (AHCPR 1999): compared with SSRIs, TCAs resulted in significantly higher rates of dry mouth (rate difference [RD] 30%), constipation (RD12%), dizziness (RD11%), blurred vision (RD 4%) and tremors (RD 4%). Compared with TCAs, SSRIs resulted in significantly

higher rates of diarrhea (RD 10%), nausea (RD 10%), insomnia (RD 7%) and headache (RD 3%). Fewer patients taking SSRIs or reversible MAO-A inhibitors discontinued treatment because of adverse effects compared with TCAs (AHCPR 1993).

2.1.3 *Specific clinical features influencing the treatment plan*

The degree of benefit from adequate treatment appears to increase with severity of depression. For mild depressive episodes, the benefit of treatment with antidepressants is uncertain; education, support and problem solving are treatment alternatives (Anderson et al 2000). Individuals with a major depressive episode frequently present with features and symptoms in addition to those required to meet the DSM-IV (or ICD-10) criteria (Table 1). There is some indication that the different subtypes of major depression respond differentially to the various classes of antidepressants.

MDD with Melancholic Features (typical features include loss of pleasure in all or most 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 dissimilar to 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" necessarily have melancholic features. Hospitalized patients also frequently present with melancholic features. According to meta-analyses, 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 (Level A). 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 amitryptiline and clomipramine, as well as venlafaxine, may be more effective than the SSRIs in the treatment of patients with severe melancholic depression (Perry 1996; Anderson 2001).

MDD with Atypical Features (typical features are mood brightening in response to events, hypersomnia, weight gain, intense fatigue, leaden heaviness of limbs, rejection sensitivity as a personality trait): There is some evidence that depressed patients with atypical features particularly benefit from the irreversible MAOIs (Level B) (Quitkin et al 1991; Nierenberg et al 1998a). 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).

Suicidal Depression: Suicide is a major risk in patients with major depression. The suicide risk should be assessed initially and regularly over the course of treatment (frequency of such assessment depends on the severity of suicidality, presence of risk factors for suicide, and treatment setting). The following factors are associated with a high suicide risk: affective illness, poor impulse control, gender (males between age 20 and 30 and over age 50 years; and females between age 40 and 60), history of previous suicide attempt, 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 1999b; Bostwick and Pankratz 2000). If the patient has suicidal thoughts or intent, close surveillance is necessary and admission to a psychiatric ward should be considered. Hospital admittance without patient consent may be necessary. Immediate and intensive care should be initiated and should include aggressive pharmacotherapy and psychotherapy that addresses psychosocial factors. A specific, acutely acting "anti-suicidal" medication does not exist, but it is recommended not to use an antidepressant that will increase agitation (Table 4). Many clinicians have successfully added a neuroleptic or benzodiazepine (Furukawa et al 2001) medication to the treatment regimen. For patients considered likely to take an overdose, it is recommended that only one week's supply of potentially lethal antidepressants (e.g., the TCAs or irreversible MAO inhibitors) be prescribed at a time, and that the antidepressant chosen is one that is safer in cases of overdose (Table 4; AHCPR 1993). In cases of severe suicidality, early ECT may be considered (Chapter 2.3). There is also some indication that lithium has "anti-suicidal" activity when administered prophylactically (see Part 2 of these guidelines (Bauer et al In Press)).

For information on treatment recommendations for *MDD with Psychotic Features (Delusional Depression),* see Chapter 2.6.1 (Antipsychotics); for *MDD with Seasonal Pattern,* see Chapter 2.5 (Light Therapy); and for *MDD with Anxiety Features* ("Anxious" Depression), see Chapter 4.1.1 (Anxiety Disorders).

2.1.4 *Evaluating the efficacy of the initial treatment*

To evaluate the efficacy of the initial treatment, it is necessary to administer an antidepressant for a defined period and then to perform a reasonable assessment of the patient's response (this may include the use of patient self-rating scales and/or observer-ratings scales, e.g. the Clinical Global Impressions scale [CGI; Guy 1976], the Hamilton Rating Scale for Depression [HRSD; Hamilton 1960], the Montgomery-

Åsberg Depression Rating Scale [MADRS; Montgomery and Åsberg 1979], or the Bech-Rafaelsen Melancholia Scale [BRMS; Bech and Rafaelsen 1986]) (Rush and Kupfer 2001). To clarify the relevant terms of treatment response, the following criteria are suggested:

- Nonresponse: ≤ 25% decrease in baseline symptom severity
- Partial response: 26%-49% decrease in baseline symptom severity
- Response: ≥ 50% decrease in baseline symptom severity
- Response with residual symptoms: response with partial remission
- Remission: absence of symptoms defined by absolute scale score (sometimes called full response or full remission).

Growing evidence indicates that acute-phase medication trials should last at least six weeks, and eight to 10 weeks to define the full extent of symptom reduction (Rush and Kupfer 2001). It should be emphasized that responders do not always remit (only approximately two-thirds of nonresistant responding depressions remit in eight week trials). Koran et al (2001) showed that 40% of responders eventually remit during the continuation phase of treatment. If the initial treatment must be discontinued due to intolerable side effects, a switch to a different treatment is called for (for additional treatment options, see below).

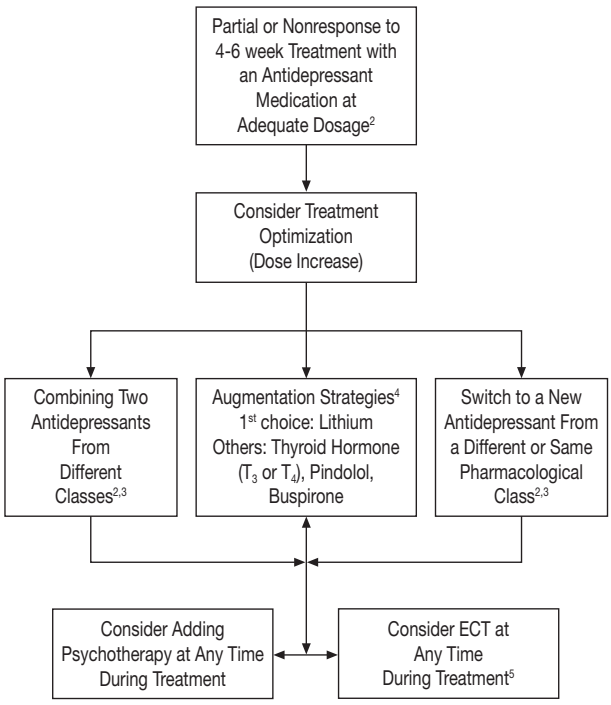
2.1.5 *When to declare initial treatment failure*

The physician must decide when to discontinue the current medication. Changing the treatment strategy too early may lead to false conclusions, e.g., that the medication is ineffective, and discourage the patient. In contrast, persisting over too long a period without any response may lead to unnecessary prolongation of the patient's suffering and duration of the episode. Thus, it seems crucial to choose the right moment to consider a change in the treatment plan.

If the patient is not showing any improvement after four weeks of treatment with an antidepressant at an appropriate dose (Table 3), it becomes less likely that he/she will respond to this particular medication later. If the patient is showing a partial response after four to six weeks, it becomes more likely that the patient will respond after eight to 12 weeks of therapy. Data from a controlled trial of fluoxetine have suggested that if the patient has not had at least a 20% to 25% reduction in symptom severity by four weeks, then the likelihood of a response at eight weeks is about 20% (Nierenberg et al 1995). There is some evidence that older adults may take longer to show a response to antidepressant medications (up to 12 weeks). This may be particularly true with fluoxetine because of its very long half-life, achieving a steady state only after four to six weeks. In cases with a partial response, where features of personality disorders and psychosocial stressors are prominent, an extension of the treatment trial by two to four weeks has been recommended (Frank and Kupfer 1990).

2.1.6 *Diagnostic reassessment and optimizing antidepressant medication*

Before considering a switch in the treatment strategy, a first step should be a reappraisal of the diagnosis and adherence to the current treatment regimen. Patient adherence to medication should be analyzed, and in the case of non-adherence, its reasons should become a focus of therapeutic intervention. Pharmacokinetic factors affecting plasma levels of antidepressants may also be taken into consideration. If available, plasma levels of tricyclic antidepressants can be helpful in evaluating the adequacy of a trial using these medications (see below and Table 3). A review of the findings from physical examinations and laboratory results is wise to avoid overlooking coexisting general medical conditions, non-psychiatric medications, or hidden substance abuse that may underlie or be associated with the depressive episode. Persistent psychosocial stressors should also be taken into consideration as a reason for nonresponse to treatment. Reevaluation of the adequacy of the medication dose is also advised. An optimization



[1] partial response: 26%-49% decrease in baseline symptom severity; nonresponse: ≤ 25% decrease in baseline symptom severity
[2] see Table 3
[3] caution with combining irreversible MAO inhibitors (see Chapter 2.1.9.1, 2.1.9.3)
[4] see Table 5
[5] for indications see Chapter 2.3

Figure 1
Flow chart - Therapeutic options in partial and nonresponders[1] to initial treatment with an antidepressant in major depressive disorders

of the treatment may be achieved by increasing the dose of the antidepressant, particularly in patients who have received only a moderate dose (Figure 1).

2.1.7 *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 and compliance 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 (at least in some TCAs; for ranges see Table 3; Perry et al 1994), evaluating toxic effects and monitoring for unwanted drug-drug interactions. Specifically, TDM may identify the subgroup of patients who are at risk of developing excessive plasma TCA levels that may potentially result in central nervous system and cardiovascular toxicity (Preskorn and Fast 1991; Perry et al 1994; Brøsen 1996).

Unlike some TCAs, there is no clear relationship between clinical efficacy and plasma concentration of the SSRIs, nor any threshold that defines toxic concentrations. Therefore routine monitoring of SSRI plasma levels cannot be recommended. TDM of the SSRIs, however, may influence clinical dosing strategies and thus reduce drug costs in depressed elderly patients (Lundmark et al 2000). Moreover, it should be considered that depression is a significant risk factor of noncompliance with medical treatment (DiMatteo et al 2000). TDM may therefore be useful in situations where poor compliance is suspected and when therapeutic failure or toxic events are experienced at clinically used dosages (Rasmussen and Brøsen 2000).

2.1.8 *Pharmacokinetics and pharmacogenetics of antidepressants*

Plasma concentrations and response to 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, CYP2D6 and CYP3A4 are most importantly responsible 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 SSRIs (Brøsen 1998).

"Slow" ("poor") metabolizers are individuals who possess no or limited activity of a CYP450 isoenzyme as a result of genetic polymorphism (genetic polymorphism exists if a CYP450 gene with a variant allele is present in at least 1% of the population). "Rapid" ("fast" or "extensive") metabolizers are individuals who have one or more CYP450 isoenzyme that biotransforms at an accelerated rate 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). However, only 10% to 30% of the ultrarapid metabolizer phenotypes may be diagnosed for duplicated alleles (Løvlie et al 2001). Further research is needed to characterize the majority of ultrarapid metabolizers. 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). In some patients suggested as noncompliant (as a consequence of low drug plasma levels despite high doses), a combination of TDM and genotyping may be informative. Genetic analyses (genotyping), suitable for routine laboratories, are now available in some countries for the analysis of important metabolizing enzymes (e.g., CYP2D6, CYP2C19). Such analyses can aid in the identification of those individuals who are slow or rapid metabolizers of certain antidepressants (Bertilsson et al 1997; Tanaka and Hisawa 1999; Steimer et al 2001).

Pharmacokinetic drug-drug interactions may occur when drugs metabolized by the same CYP450 isoenzyme interact. The first 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. The second 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).

SSRIs vary widely in their qualitative and quantitative interaction with CYP450 isoenzymes. CYP2D6 is inhibited by SSRIs (in order of decreasing potency: paroxetine, norfluoxetine and fluoxetine) (Hiemke and Härtter 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, both of 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. If SSRIs that are inhibitors of CYP isoenzymes are combined with TCAs, the dose of the TCA should be lower than usual, and plasma TCA concentrations should be monitored during the course of treatment. Although the "newer" antidepressants (venlafaxine, mirtazapine or reboxetine) are also metabolized through the CYP450 systems, they are associated with low drug-drug interactions compared to SSRIs (Kent 2000).

2.1.9 *Treatment options for the partial and nonresponding patient*

Regardless of the initial choice of antidepressant, about 30% to 50% of depressions will not respond sufficiently to treatment (Thase and Rush 1995). Various treatment strategies have been proposed for the depressions not or only partially responding to a first adequately performed trial with an antidepressant (Amsterdam 1991; Nolen et al 1994). The major types of strategies employed are: (1) switching to a new antidepressant from a different pharmacological class (e.g., from a SSRI to a TCA); (2) switching to a new antidepressant within the same pharmacological class (e.g., from an SSRI to another SSRI); (3) combining two antidepressants from different classes (e.g., a TCA plus a SSRI); (4) augmenting the antidepressant with other agents (e.g., lithium or thyroid hormone) to enhance antidepressant efficacy; and (5) combining the antidepressant with a psychotherapeutic intervention(Chapter 2.4.1). These strategies have been studied with a variety of agents and combinations, but most of these have not been subjected to rigorous scientific investigation, or have included small study groups. Furthermore, most of the combination treatments used are derived from theoretical viewpoints and are not 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.

Currently, there is no clear consensus which strategy should be favoured for the non-responding patient since to date no rigorous trial with a randomized, double-blind design has been conducted to answer this question (Crismon et al 1999). Some authors have argued to favour augmentation strategies because, in contrast to other strategies, some of the augmentation strategies, e.g., lithium, have repeatedly been investigated in placebo-controlled trials. The level of evidence, advantages and disadvantages of the different treatment strategies for the partially or non-responding patient will be reviewed in the following.

2.1.9.1 *Strategy 1: Switching to a new antidepressant from a different class*

With the introduction of an increasing number of different classes of antidepressants, switching to a different antidepressant agent has become a common strategy in treatment failures to the initial antidepressant (Crismon et al 1999). For depressions that show no response, switching to an antidepressant in another class with a different mechanism of action may be beneficial. When SSRI and TCA are involved, about 50% of patients who do not respond to one class will respond to the other (Level B) (Thase and Rush 1995). There is also evidence that depressions that fail to respond to a TCA may benefit substantially from an irreversible MAO inhibitor (Level B) (AHCPR 1993).

The advantage of this strategy is that it minimizes polypharmacy, which helps prevent toxicity and negative drug-drug interactions, and may enhance patient adherence. Switching may also lead to fewer or more tolerable side effects. One of the disadvantages is the loss of partial efficacy by switching from the initial antidepressant, and the relatively long period until the second agent can develop its antidepressive activity (delayed onset compared to augmentation or combination). It is recommended that the first antidepressant be tapered off slowly rather than abruptly discontinued, for this may cause withdrawal symptoms, particularly if the medication has been administered for a longer period. Switching from or to an irreversible MAO inhibitor should be performed with caution and with a two-week wash-out period between the two drugs.

2.1.9.2 *Strategy 2: Switching to a new antidepressant 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% to 70% chance of responding to a second SSRI

(Level C) (Thase and Rush 1997). Switching from one TCA to another has not been well studied and results have not been promising (response rates between 9% and 27%) (Nelson 1998).

2.1.9.3 Strategy 3: Combining two antidepressants 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 abandoning partial response with a monotherapy, and fear of worsening of depressive symptoms when a partially effective medication is discontinued. Disadvantages of this strategy include the increased risk of drug-drug interactions, potentiation of side effects and drug costs.

Although often applied in clinical practice, there is little controlled data in support of the utility and efficacy of this strategy (Level C, applies to all combinations). 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). Among the combinations of non-TCA antidepressants, augmentation of fluoxetine with mianserin was effective and safe in two controlled studies (Dam et al 1998; Ferreri et al 2001). Combination of various SSRIs with mirtazapine showed promising results in open-label studies (Carpenter et al 1999). Adding an SSRI to a TCA can cause an increased blood level and delayed elimination of the tricyclic antidepressant leading to an increased risk of tricyclic medication toxicity (Chapter 2.1.8). Combining irreversible MAO inhibitors with SSRIs and other antidepressants acting on the serotonergic system (e.g., clomipramine, venlafaxine) must be strictly avoided due to potentially fatal interactions (serotonin syndrome). Similarly, combinations of an SSRI with L-tryptophan should be avoided.

2.1.9.4 Strategy 4: Augmentation of antidepressants

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. Augmentation strategies have some advantages. One advantage

Table 5
Biological treatment strategies for partial and nonresponding patients with major depressive disorders

Treatment Strategy	Mechanisms /Drug Classification	Level of Evidence[a]	Reference/Review
Pharmacological Augmentation[b]			
Lithium	Mood Stabilizer	A	Bauer & Döpfmer 1999
Valproate, carbamazepine	Anticonvulsants/Mood stabilizer	C	Dietrich & Emrich 1998
Pindolol	5-HT_{1A} autoreceptor antagonist, beta-receptor blocker	C	Perez et al 1999
Buspirone	5-HT_{1A} and D_2 receptor agonist	C	Landén et al 1998
Stimulants	Dopamine and noradrenaline release and reuptake inhibition	C	Nierenberg et al 1998b
Bromocriptine	Dopamine (D2) agonist	C	Inoue et al 1996
Pergolide	Dopamine (D1/D2) agonist	C	Boukoms & Mangini 1993
Reserpine	Reuptake inhibition of biogenic amines	C	Zohar et al 1991
Olanzapine, risperidone	Antipsychotic agents 5-HT_2 antagonism	C	Shelton et al 2001b, Ostroff & Nelson 1999
Hormone Augmentation			
Triiodothyronine (T_3)	Thyroid hormone	B	Aronson et al 1996
L-Thyroxine (T_4)	Thyroid hormone	C	Bauer & Whybrow 2001
Estrogen (only women)	Ovarian steroid hormone	C	Sherwin 1991
Dehydroepiandrosterone (DHEA)	Adrenal androgen hormone	C	Wolkowitz et al 1999
Miscellaneous			
Ketokonazole, metyrapon	Peripheral cortisol suppression	C	Wolkowitz & Reus 1999
L-Tryptophan	Essential amino acid, 5-HT precursor	C	Young 1991
Non-Pharmacological			
Electroconvulsive therapy (ECT)	Electric stimulation to elicit an epileptiform seizure in brain	A	Nobler & Sackeim 2000
Repetitive transcranial magnetic stimulation (rTMS)	Noninvasive stimulation of the cerebral cortex	C	Pascual-Leone et al 1996
Vagus Nerve Stimulation (VNS)	Autonomic signals to limbic and cortical function	D	Rush et al 2000

[a] see Chapter 1.4
[b] does not include combinations of antidepressants (see Chapter 2.1.9.3)

is that they eliminate the period of transition from one antidepressant to another and build on the partial response. Consequently, when they work, augmentation strategies can be rapidly effective. Secondly, patients who have had some response may be reluctant to risk losing that improvement, and, in this situation, augmentation may be beneficial. Numerous augmentation strategies have been described for use in treatment-resistant depression. Table 5 summarizes the major pharmacological augmentation strategies and presents the levels of documented empirical evidence of the efficacy for each of these strategies.

2.1.9.4.1 Lithium

Among those strategies listed in Table 5, lithium is the foremost and most well-documented augmentation strategy, with more than 27 open studies and 10 placebo-controlled trials in the acute treatment phase of major depression (Level A). Thus, adding lithium to ongoing antidepressant treatment is recommended as the first choice of an augmentation strategy. 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 SSRIs (Katona et al 1995; Baumann et al 1996; Zullino and Baumann 2001). A meta-analysis including nine placebo-controlled studies has confirmed that lithium augmentation is superior to placebo augmentation in unipolar major depression, with response rates of about 40% to 50% across studies (Bauer and Döpfmer 1999). About 20% of patients have been reported to respond during the first week. Lithium augmentation should be administered for two to four weeks to allow assessment of the patient's response. The recommended lithium doses (600-1200 mg/day of lithium carbonate) characteristically achieve serum lithium levels of 0.6 to 0.8 mmol/L.

2.1.9.4.2 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, with most studies employing 25 to 37.5 mcg/day to potentiate the response to tricyclic antidepressants in nonresponders (Level B) (Joffe et al 1993; Bauer and Whybrow 2001). The open studies consistently showed that about 50% of TCA nonresponders are converted to responders within two to three weeks after the addition of T_3. A three-armed, double-blind, controlled study showed equal efficacy of augmentation with T_3 and lithium compared to placebo (Joffe et al 1993). However, not all controlled double-blind studies yielded significant results in favour of T_3. Subsequently, a meta-analysis did not find consistent results in favour of T_3 augmentation (Aronson et al 1996). Furthermore, the efficacy of T_3 augmentation with today's widely used non-tricyclic antidepressants, e.g., SSRIs, has only been studied in one case series. 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) (Level C) (Bauer et al 1998). The use of thyroid hormones is particularly recommended for patients with subclinical hypothyroidism (defined as an abnormally high TSH level, but normal peripheral thyroid hormone levels).

2.1.9.4.3 Other pharmacological augmentation strategies

The treatment of patients with major depression using 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). To a lesser extent, this strategy has also been studied as an augmentation strategy in patients with treatment-resistant depression, but results have been contradictory (Level C) (Maes et al 1996; Perez et al 1999).

The serotonin precursors, L-tryptophan and 5-hydroxytryptophan (5-HTP), have been studied in depressive disorders with equivocal results (Mendels et al 1975; Byerley et al 1987; Young 1991; Shaw et al 2001). Some small trials using L-typtophan showed potentiation of MAOIs and augmentation of serotonergic antidepressants in refractory depressed patients (Level C) (Coppen et al 1963; Glassman and Platman 1969; Ayuso Gutierrez and Alino 1971).

In contrast to its use for treating psychotic depression (Chapter 2.6.1), the use of antipsychotics to augment antidepressants in nonpsychotic major depression has recently increased in clinical practice. There is one small placebo-controlled study of olanzapine that supports this strategy in treatment-resistant nonpsychotic major depression (Level C) (Shelton et al 2001b).

Many other augmentation strategies with different pharmacological profiles and targets have been studied to a lesser extent. However, for all of these strategies, placebo-controlled trials in treatment-resistant depressed patients are lacking (Coryell 2000) (for level of evidence and further reading see references in Table 5).

2.1.10 Treatment-resistant depression

As many as 50% of nonresponders to a first antidepressant trial also fail to respond to a second, different course of treatment. A residual group of patients remain depressed and do not achieve adequate relief and a satisfactory level of functioning even after two or more adequate courses of treatment. Having failed to improve after two adequately performed antidepressant trials, these nonresponders are considered "treatment-resistant". While many of them may be helped by the treatment strategies that have

been described above (Nierenberg and Amsterdam 1990; Möller 1994; Nemeroff 1996-97; Burrows and Norman 1999), 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 (Montgomery 1991; Nierenberg and Amsterdam 1990; Guscott and Grof 1991; Bauer and Helmchen 2000). Some studies indicate that only a minority of treatment-resistant patients are "absolute" resistors, and the majority of "relative" resistors can be helped substantially by rigorous treatment approaches, including a course of electroconvulsive therapy (ECT) (Adli et al 2002). Patients with a history of positive response to ECT may be candidates for immediate ECT when a new episode requires treatment.

Repeated drug trials that are not adequately performed 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 has suggested that the probability of responding to an antidepressant declines by a factor of approximately 15% to 20% for each prior failed drug treatment (Amsterdam et al 1994). 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, 1999). Treatment algorithms are supposed to be key instruments in improving adherence to antidepressant regimens and in optimizing the execution of treatment in terms of treatment effectiveness and cost efficiency. Such algorithms have been proposed, but to date have rarely been rigourosly studied in controlled trials (Level D) (Katon et al 1995; Gilbert et al 1998; Hawley et al 1998; Rush et al 1999; Bauer and Helmchen 2000; Adli et al 2002).

2.2 Herbal remedies

For patients who are reluctant to take traditional antidepressants, herbal remedies are a potential alternative. However, evidence of herbal remedy efficacy is incomplete for the treatment of major depression, particularly severe depression, and for the long-term treatment of depressive disorders (Williams et al 2000).

There is evidence from a substantial number of controlled trials which suggests that extracts from the plant Hypericum perforatum (popularly called St. John's wort) are more effective than placebo for the short-term treatment of mild to moderately severe depressive disorders (Level A) (Kim et al 1999; Williams et al 2000; Linde and Mulrow 2001). A meta-analysis of hypericum for depressive disorders, including 14 trials with 1417 patients, confirmed the herb's superior efficacy compared to placebo treatment (Williams et al 2000). However, a recent placebo-controlled, multi-center 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, from the available data St. John's wort cannot be recommended for the treatment of severe depression.

The standard dose of hypericum (St. John's wort) is 600-900 mg/d. Adverse effects appear to occur less frequently with St. John's wort, compared to tricyclic antidepressants (Kim et al 1999). There is little information on the herb's medium- to long-term efficacy and side effects (AHCPR 1999; Linde and Mulrow 2001). There is evidence that hypericum can interact with a number of prescription drugs (for example, it can decrease blood levels of TCAs and antiretroviral medications used in the treatment of HIV infection). Health care providers should consider this fact when their patients take hypericum or other herbal substances. Also, there have been concerns about the purity and variable potency of the herbal remedies.

2.3 Electroconvulsive therapy

Electroconvulsive therapy (ECT) involves an electrical stimulus to elicit a therapeutic, epileptiform 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 (TCAs) (Level A) (American Psychiatric Association Task Force on Electroconvulsive Therapy 1990; AHCPR 1993; American Psychiatric Association 2000). ECT is associated with a 60% to 80% remission rate, with maximum response typically achieved after two to four weeks (Kennedy et al 2001). However, there are few data comparing ECT with SSRIs and the newer antidepressants (Wijeratne et al 1999).

Among the indications for ECT as a first-line treatment are severe major depression with psychotic features, severe major depression with psychomotor retardation, "true" or "absolute" treatment-resistant major depression, refusal of food intake, or other special situations when rapid relief from depression is required (e.g., in severe suicidality or in pregnancy) (American Psychiatric Association 2000). 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.

ECT is increasingly combined with antidepressants to improve acute-phase response, although only little data exists supporting this practice (Level D) (American Psychiatric Association 2000). One disadvantage of ECT is that without follow-up treatment its effects only last for a few months. 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 six months. In a controlled study of the post-ECT phase, paroxetine was shown to be superior to both imipramine and placebo in preventing relapse (Level C) (Lauritzen et al 1996). Medication resistance and greater severity of depression pre-ECT has also been shown to predict relapse. Thus, medication used unsuccesfully prior to ECT should not be used to prevent post-ECT relapse (Bourgon and Kellner 2000; Nobler and Sackeim 2000).

Although ECT is a very effective treatment procedure, it is not recommended as first-line therapy for uncomplicated, nonpsychotic depressed patients due to the potential anaesthetic risks. 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. Prior to treatment implementation, a thorough medical evaluation of the patient must be performed in close collaboration with an anesthesiologist. Caution is indicated in patients with evidence of increased intracranial pressure or cerebrovascular fragility, and in patients with cardiovascular disease, e.g., recent myocardial infarction, myocardial ischaemia, congestive heart failure, cardiac arrhythmias or pacemakers, or abdominal aneurysm (American Psychiatric Association 2000). ECT may only be performed by a psychiatrist who is experienced with this treatment intervention.

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 credible evidence that ECT causes structural brain damage (Devanand et al 1994).

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 (Bauer et al In Press)). 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). Unilateral electrode placement requires an electrical dose six times the seizure threshold (defined as the lowest electrical dosage necessary to produce adequate generalized seizure) to have the same efficacy as bilateral placement (Sackeim et al 1987). 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.

2.4 Psychotherapy

As mentioned earlier, these guidelines focus on biological (somatic) treatments of major depressive disorder. Therefore, psychotherapeutic treatments alone or in combination with pharmacotherapy will only be mentioned briefly and no levels of evidence are provided. Instead, references for further reading are given.

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. Psychotherapy should be considered as an initial treatment modality for patients with mild to moderate depression, and in combination with antidepressants for patients with more severe forms of depression and patients who have had partial responses to antidepressant medications or who have had problems with adherence to antidepressants (Rush and Thase 1999). 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.

A number of brief, structured psychotherapies 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 (six to 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) (Beck et al 1979; Glogauen et al 1998; Dobson 1989; Gaffan et al 1995; Blackburn and Moore 1997; DeRubeis et al

1999; Hollon et al 1992), behavioural therapy (Rehm 1979; Bellack and Hersen 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), and the cognitive behavioural analysis system of psychotherapy (CBASP) (McCullough 2000). There is less empirical evidence for the efficacy of other types of psychotherapy (for example psychodynamic psychotherapy), but this does not mean that such treatments do not work.

Problem solving treatment (PST) has been shown in one randomized controlled trial to be an effective treatment for depressive disorders in primary care (Mynors-Wallis et al 2000). PST can be delivered by non-specialists after training and is therefore a cost-effective alternative to formal psychotherapies, which are often not rapidly or not at all available in primary care settings of many countries.

2.4.1 *Combining antidepressants with 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 et al 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, there is relatively little evidence from RCTs in support of such combined treatment (Rush and Kupfer 2001). A recent 12-week study of nefadozone treatment, the cognitive behavioural analysis system of psychotherapy (CBASP) (administered for 16 to 20 sessions), and the use of both in combined treatment indicates that the combined treatment is significantly more efficacious than the use of either treatment alone in outpatients with chronic forms of major depressive disorder (DSM-IV) (Keller et al 2000). A meta-analysis of 595 patients from six randomized treatment protocols who had been diagnosed with major depression and were receiving either cognitive behavioural therapy, interpersonal psychotherapy (IPT) or IPT plus antidepressant pharmacotherapy (combined therapy), produced evidence in support of the widespread clinical impression that combined therapy is superior to the use of psychotherapy alone for treatment of severe, recurrent depressions (Thase et al 1997). There is also evidence that patients find combined treatment more acceptable and that they are less likely to drop out of combined therapy compared to treatment with an antidepressant alone (de Jonghe et al 2001).

2.5 Light therapy (Phototherapy)

Seasonal affective disorder (SAD) is a distinct subtype of recurrent major depression that occurs with a seasonal pattern (Rosenthal et al 1984; American Psychiatric Association 1994). It has been estimated that it affects about 5% to 10% of the general population, predominantly women (Kasper et al 1989; Rosen et al 1990). "Winter" depression, in which patients experience symptoms of clinical depression during autumn and winter, with full remission during the spring and summer seasons, is the most common type of SAD.

Light therapy (phototherapy) or treatment with SSRIs is the treatment of first choice for SAD (Level A) (Lam et al 1995; Ruhrmann et al 1998; Lee and Chan 1999). A series of studies has demonstrated the efficacy and good tolerability of bright (artificial) light therapy over nonlight control conditions in "winter" depression (Level A) (Eastman et al 1998; Terman et al 1998; Lewy et al 1998). The fluorescent light box, which provides white, fluorescent light with ultraviolet wavelengths filtered out and which produces light intensities greater than 2,500 lux, is the preferred device for light therapy. The starting "dose" for light therapy is 10,000 lux for 30 to 40 minutes per day, administered each morning for a two to four week period. Alternatively, light boxes emitting 2,500 lux require two hours of exposure per day (Lam and Levitt 1999). Correct positioning (sitting close enough to the light box) is important. Patients usually show improvement within one week, but it takes up to four weeks until the full response is achieved. If a light box is not available, "natural light treatment" may be administered in patients with SAD by a daily one-hour outdoor morning walk for two weeks or more (Wirz-Justice et al 1996).

The results of studies assessing the efficacy of light therapy in nonseasonal depression have been controversial. As a result, light therapy has only been suggested as an adjunct treatment in chronic major depressive disorder or dysthymia with seasonal exacerbations (Level D) (American Psychiatric Association 2000).

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 ophthalmologic consultation. The common side effects of light therapy reported by patients in clinical trials include eye strain or visual disturbances, headache, agitation or feeling "wired", nausea, sedation, and very rarely hypomania or mania. These side effects are generally mild and transient and resolve with time or with the reduction of the light dosage (Lam and Levitt 1999). "Natural light treatment" may be inconvenient at higher geographical latitudes. 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 (American Psychiatric Association 2000) (a comprehensive review on SAD is provided by the Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder (Lam and Levitt 1999)).

2.6 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. Many of these treatments may help to accelerate the response to the primary antidepressant treatment, to control anxiety/insomnia and to reduce other depressive symptoms until full recovery is achieved.

2.6.1 *Antipsychotics*

Major depressive disorder may be associated with delusions and/or hallucinations; these may be congruent or noncongruent with the depressed mood (American Psychiatric Association 2000). Patients with major depressive disorder and psychotic features have a considerably better response rate to the combination of an antidepressant plus an antipsychotic than to treatment with either component alone (Level A) (Spiker et al 1985; Rothschild et al 1993). In these patients, it is recommended to combine an antidepressant with an antipsychotic medication at the beginning of treatment initiation (Level A). The newer, "atypical" antipsychotics (e.g., amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) may be preferred to the “classic” antipsychotics (e.g., chlorpromazine, fluphenazine, haloperidol, perazine) or clozapine in terms of their favourable side effect profile and tolerability. However, there are no controlled data from comparisons of the "newer" with the "older" antipsychotics in psychotic depression. Usually the administered doses of antipsychotics are lower in depressed patients than those used in schizophrenia. Because some antipsychotic drugs (thioridazine and droperidol) and tricyclic antidepressants may cause ECG changes (QTc lengthening), these drugs may increase a patient’s risk of drug-induced arrhythmia, especially when administered in combined treatment and to older patients (Reilly et al 2000).

2.6.2 *Tranquilizer/anxiolytics*

Most randomized controlled trials have shown that benzodiazepines, with the possible exception of some triazolo-benzodiazepines, e.g. alprazolam, for mild to moderate depression, are less effective than standard antidepressants in treating major depression (Level A) (AHCPR 1993). Although tranquilizers (especially benzodiazepines) are frequently used as adjunctive medication in clinical practice worldwide, it is believed by many experts that the depressive state is not improved with benzodiazepines. A recent review reported that in most countries between 30% and 60% of depressed patients are co-administered an antidepressant and a tranquilizer (Furukawa et al 2001). The reason for this practice is most likely the fast onset of action that reduces anxiety, agitation and insomnia in many patients, and the high rate (between 33% to 85% across studies) of anxiety comorbidity among patients with major depression.

A meta-analysis including nine randomized placebo-controlled trials showed that the combined antidepressant-benzodiazepine treatment is more likely to produce response than the antidepressant alone (63% vs. 38%). It also showed that patients in the combination group were 37% less likely to drop out than patients in the antidepressant alone group (Level A) (Furukawa et al 2001).

In each individual patient, the potential benefits of adjunctive treatment with benzodiazepines must be carefully balanced against possible harm (including sedation, psychomotor and cognitive impairment, memory loss, potentiation of other central nervous system depressants and treatment-emergent depression, development of dependence, and discontinuation syndromes). Predisposed individuals are at greater risk of developing dependency and tolerance. Thus, 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 be restricted to a maximum period of approximately four weeks. Short- and intermediate-acting benzodiazepines carry a greater risk of rebound and withdrawal reactions and drug dependence, compared to long-acting agents (Nelson and Chouinard 1999).

Adjunctive treatment with the anxiolytic agent buspirone, a 5-HT_{1A} partial agonist without obvious risk for developing dependency, may be useful to control anxiety in depressed patients (Level C) (Davidson 2001).

2.6.3 *Sleep deprivation*

Total or partial sleep deprivation (SD) may be the only antidepressant intervention with marked beneficial same-day effects providing transient amelioration of depression in about 60% of patients (Level A) (Kuhs and Tölle 1991; Wirz-Justice and Van den Hoofdakker 1999). Sleep deprivation alone, preferentially total SD, may be used to treat an unmedicated depressed patient, 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 (Van den

Hoofdakker et al 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 acts rapidly, 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). Usually, the antidepressant effect can be replicated by repeated total sleep deprivation (Level C) (Wiegand et al 2001) or by combining sleep deprivation with a subsequent phase advance of the sleep period (Level D) (Riemann et al 1999). Other strategies to sustain the antidepressant effect include combining SD with lithium, pindolol or thyroid hormone (Level D) (Wirz-Justice and Van den Hoofdakker 1999).

2.6.4 *Exercise training*

There is indication from studies of healthy young people that physical activity may have positive effects on mood. Open studies of the short-term effects of an adjunctive daily aerobic exercise program suggested relatively rapid (by day 14) mood improvements in patients with major depression (Dimeo et al 2001). A 16-week RCT that included 156 elderly patients with MDD compared sertraline with an aerobic exercise program and found at the study's end that exercise was as effective as sertraline but that the sertraline group had a faster onset of response (Blumenthal et al 1999). However, a recent meta-analysis concluded that the effectiveness of exercise in reducing symptoms of depression cannot be determined to date because of a lack of good quality research on clinical populations (Lawlor and Hopker 2001). Thus, further controlled trials in major depression are needed to better understand the role of exercise as an adjunct therapy or monotherapy for reducing symptoms of depression (Level C).

2.7 Novel therapeutic strategies

2.7.1 *Transcranial Magnetic Stimulation (TMS)*

Transcranial Magnetic Stimulation (TMS) is a new technology for noninvasively stimulating cortical neurons by magnetic induction using a brief, high-intensity magnetic field (Pascal-Leone et al 1996; George et al 1999; McNamara et al 2001). Preliminary controlled studies have shown that repetitive TMS (rTMS) used to stimulate the left prefrontal cortex daily for two weeks leads to mood improvement in patients with major depression (George et al 1997; George et al 2000). One controlled study of 70 patients with recurrent major depression reported evidence for the short-term efficacy of right prefrontal rTMS (Klein et al 1999).

In 18 patients with treatment-resistant major depression, a double-blind controlled study showed that left prefrontal rTMS does not provide significantly greater improvement than did sham treatment (Loo et al 1999). However, a two-week course of left prefrontal rTMS resulted in statistically significant, but clinically modest, reductions of depressive symptoms, as compared to sham rTMS, in a group with unmedicated treatment-resistant major depression (Level C) (Berman et al 2000).

The side effects and the long-term changes in brain function of rTMS are largely unexplored. Provocation of epileptic seizures has been described in rare cases (Wassermann 2000).

2.7.2 *Vagus Nerve Stimulation (VNS)*

Vagus Nerve Stimulation (VNS) is a new technology for indirect brain stimulation that has been commercially available in Europe since 1994 and in the United States since 1997 for treatment-resistant epilepsy (George et al 2000). It involves implanting a pacemaker and connecting it to the left vagus nerve, which sends autonomic electrical signals via the midbrain to limbic and cortical areas. VNS showed promising results in one trial of treatment-resistant depressed patients (Level D) (Rush et al 2000).

2.7.3 *Steroid-lowering drugs and CRH receptor antagonists*

It is well established that the hypothalamic-pituitary-adrenal (HPA) "stress" system is hyperactive in major depression, which is reflected by peripheral changes of ACTH and cortisol homeostasis. A central corticotropin-releasing hormone (CRH) hypersecretion has been postulated as the underlying mechanism of the HPA system hyperactivity in depression (Nemeroff et al 1984; Holsboer 2000). Subsequently, it has been suggested that the HPA system may be an appropriate site for peripheral (steroid-lowering or antiglucocorticoid drugs) and central pharmacological intervention in the management of depression (Barden et al 1995). There is evidence from a series of open-label trials and small double-blind trials that various corticosteroid synthesis-blocking agents (aminoglutethimide, ketoconazole, metyrapone) may be of clinical benefit in patients with untreated and refractory depression, as well as depression associated with hypercortisolaemic conditions (Level C) (Murphy 1997; Wolkowitz and Reus 1999). Furthermore, drugs that interfere directly with central stress hormone regulation, such as corticosteroid receptor antagonists and CRH receptor antagonists, have been suggested to be a potential new class of antidepressants (Owens and Nemeroff 1999; Holsboer 2001). A first open trial of a CRH receptor 1 antagonist yielded some promising results (Level D) (Zobel et al 2000).

2.7.4 *Substance P receptor antagonists*

Substance P is an abundant neuropeptide both in the periphery and in the brain, where it is localized in regions that coordinate stress responses and are critical for the regulation of

affective behaviour (e.g. the locus coeruleus and the amygdala) (Maubach et al 1999). Given the multiple interactions between substance P and the noradrenergic and serotonergic pathways, substance P has been suggested to be involved in the pathophysiology of depression and anxiety. In a first six-week, double-blind, controlled study comparing a substance P receptor antagonist (MK-869), a SSRI (paroxetine) and placebo in outpatients with major depression, the two active drugs showed equivalent robust antidepressant and anxiolytic effects (Level D) (Kramer et al 1998). The mechanism of the antidepressant action of substance P receptor antagonists is unknown, but preclinical studies have shown that their interaction with monoamine systems is different than the interaction seen with the use of established antidepressant drugs (Kramer et al 1998). Further clinical studies are necessary to prove the hypothesis that substance P receptor antagonists represent a new class of antidepressants or anxiolytics (Argyropoulos and Nutt 2000).

2.7.5 *Other novel approaches*

Other novel strategies in the pharmacotherapy of major depression have been suggested but not yet studied in humans, or marketed or published (Duman 1998; Nemeroff 1998; Nestler 1998; Maubach et al 1999; Altar 1999). Some of these follow more traditional pathophysiological models of depression and include the development of novel serotonin or noradrenergic receptor agonists/antagonists (e.g., selective 5-HT_{1A} receptor agonists, combined selective serotonin receptor antagonists and serotonin reuptake inhibitors; Nemeroff 1998; Maubach et al 1999). Other novel strategies target antidepressant drugs "beyond" the receptors and include the modulation of post-receptor mechanisms, e.g. the intracellular messenger cyclic adenosine monophosphate (cAMP) pathways, including the brain-derived neurotrophic factor (BDNF) system (Duman et al 1997; Duman 1998; Altar 1999).

3 Continuation-phase treatment of major depressive disorder

The objective of continuation treatment is to decrease the likelihood of relapse in the vulnerable period following symptomatic recovery (i.e. to prevent a return of the current episode of depression) (AHCPR 1993). The continuation phase of treatment is generally considered to be the six-month period of time immediately following full remission. However, some authors recommend a duration of up to nine months (Reimherr et al 1998; Hirschfeld 2001; Rush and Kupfer 2001). In general, patients with a history of long previous episodes would be candidates for continuation-phase treatment of more than six to nine months (e.g., duration of previous episode: 15 months; duration of current episode: two months; duration of successful acute-phase treatment: two months; recommended duration of continuation-phase treatment: 11 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). Also, continuation-phase treatment for psychotic depression should last longer than the treatment of nonpsychotic depression.

In placebo-controlled continuation therapy trials, relapse rates ranged from 31% to 80% for those patients who received placebo, compared with only 0 to 31% of those who received active TCA medication (Prien and Kupfer 1986; Prien 1990). Several continuation-phase studies involving SSRIs (citalopram, fluoxetine, paroxetine and sertraline), amineptine, nefazodone and reboxetine have been completed with 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). It is recommended that the same antidepressant successfully used to achieve relief in the acute-phase therapy be continued at the same dose during the *continuation phase* (Level A) (Thase 1999; Rush and Kupfer 2001). If no relapse occurs during continuation therapy, a gradual discontinuation of the antidepressant medication is recommended, particularly for those taking serotonin-active agents with shorter half-lives (Rosenbaum et al 1998). Patients should be carefully monitored during and immediately after discontinuation to ensure the stability of the remission (American Psychiatric Association 2000). If tapering results in a return of symptoms, the medication should be continued at the original dose for at least another six months before again attempting discontinuation.

There are a limited number of controlled trials of augmentation strategies and ECT treatment administered in the continuation phase. From these few studies, there is an indication that antidepressant treatment in addition to ECT is more efficacious during the continuation phase than the use of antidepressant treatment alone (Level B) (Gagné et al 2000).

Furthermore, after a successful course of acute-phase lithium augmentation, combined treatment using an antidepressant and lithium is suggested to be more efficacious than the combination of an antidepressant and placebo in the continuation phase (Bauer et al 2000). In another continuation-treatment study, nortriptyline-lithium combination therapy following ECT had a marked advantage in time to relapse, superior to both placebo and nortriptyline

treatment used alone (Level B for antidepressant-lithium combination in the continuation phase) (Sackeim et al 2001).

4 Treatment in special circumstances

4.1 Depression co-occurring with other psychiatric conditions

Patients with depressive symptoms or with a major depressive episode may also suffer from another (non-mood) psychiatric condition (AHCPR 1993). The most common are anxiety disorders (Zinbarg et al 1994; Boland and Keller 2000) and substance abuse/dependence (Roy et al 1991; Schuckit 1994).

4.1.1 *Anxiety disorders*

Many individuals with depression have symptoms of anxiety, and as many as 30% may have anxiety disorders (Wittchen et al 1999). Effective treatment of comorbid depression and anxiety necessitates the use of medications that have demonstrated efficacy for both conditions (Bakish 1999; Schatzberg 2000). All currently available SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) have been proven to be superior to placebo in the treatment of panic disorder and agoraphobia (Bakker et al 2000).

A number of principles should be kept in mind when treating persons who have both depression and anxiety. Depressed patients with prominent symptoms of anxiety or with comorbid anxiety disorders such as panic disorder, generalized anxiety disorder or PTSD can be treated effectively with the "newer" antidepressants (SSRIs, venlafaxine) (Level A) (Fawcett and Barkin 1998; Rudolph et al 1998), 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 as tolerated to full therapeutic doses because they can cause a transient worsening of anxiety symptoms before anxiety and depression respond to the intervention. Cognitive behavioural psychotherapy (CBT) has also been shown to be highly effective in the treatment of anxiety disorders.

In some cases, the use of a benzodiazepine anxiolytic such as diazepam, lorazepam, or clonazepam is helpful to reduce severe anxiety during the initial weeks of treatment. However, the long-term use of such anxiolytics is strongly discouraged because they can result in sedation, worsening of depressive symptoms, exacerbation of anxiety (particularly with the use of short-acting drugs), cognitive and motor impairment, psychological and physical dependence.

Obsessive-compulsive symptoms and disorders (OCD) are also common in patients with MDD. Clomipramine and SSRIs, e.g. fluoxetine and paroxetine, have demonstrated efficacy in the treatment of OCD and MDD (Level A) (Pigott and Seay 1999; Schatzberg 2000). These agents are recommended for treating depressed patients who have obsessive-compulsive symptoms or comorbid OCD (American Psychiatric Association 2000). However, SSRI doses for obsessive-compulsive symptoms and comorbid OCD are typically higher (two to three times) than the treatment doses for depression.

4.1.2 *Substance abuse/dependencies*

Depressive syndromes and substance abuse are frequently intertwined. Because this has important implications for treatment, it is essential to distinguish between a primary depressive disorder with comorbid substance abuse/dependency, and a substance-induced mood (depressive) disorder (American Psychiatric Association 1994). Research has highlighted the high prevalence (30% to 60%) of comorbid mood and anxiety disorders in patients with substance abuse/dependency. Equivalently, a third of those with affective disorder report a history of substance abuse/dependency (Regier et al 1993; Scott et al 1998).

4.1.2.1 Primary mood disorder with comorbid substance abuse

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 use in patients with depression has important implications for the treatment of depression. It can threaten the person's adherence to treatments for depression and reduce the effectiveness of depression treatments.

Persons who have depression and misuse substances often require treatment for both problems because it is rarely sufficient to treat the depression alone. Treatment options for substance misuse vary widely. It is important to be aware of local treatment options, and to refer those with drug and/or alcohol problems to the appropriate local service and/or self-help group. At times, it is prudent to initiate treatment for substance use before starting an antidepressant because symptoms of depression may remit with successful treatment of the substance use problem. Pharmacokinetic interactions from the concurrent use of methadone and antidepressants (e.g., amitriptyline) may lead to respiratory depression and sedation.

4.1.2.2 Substance-induced mood disorder

DSM-IV (American Psychiatric Association 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. The persistence of such mood disturbances is evidenced by the increased rate of depression in patients who use or are dependent on alcohol or illicit drugs such as cocaine, amphetamines or heroin. For example, in a meta-analysis, 40% of patients admitted to the hospital for alcohol abuse/dependency also

had depressive syndromes (Berglund and Nordström 1984).

Substance-induced depression is distinguished from primary major depression by the fact that a substance is clinically judged to be aetiologically related to the symptoms. Substance-induced depressions only arise during intoxication or withdrawal states, whereas primary major depression may precede the onset of substance abuse or may occur during times of sustained abstinence (American Psychiatric Association 1994). Although antidepressant pharmacotherapy may have a role in the treatment of severe disorders, the benefits of using these medications must be balanced against the increased risk of side effects or adverse reactions in individuals who continue to engage in substance misuse or who have medical complications associated with drug or alcohol dependency (Scott et al 1998). Effective psychosocial approaches focus largely on brief, empirically tested treatments, such as cognitive therapy. However, modifications are required to such approaches to ensure that the interventions are tailored to the needs of patients exhibiting comorbidity (Scott et al 1998).

4.2 Treatment of depression in children and adolescents

4.2.1 *Epidemiology, clinical characteristics and course*

A substantial proportion of patients experience their first episode of major depressive disorder during early childhood, prior to puberty or adolescence (Birmaher et al 1998). However, MDD is less common in prepubertal children (point prevalence 1.8% to 2.5%) than in adolescents (point prevalence 2.9% to 4.7%) (Brent et al 1995; Kessler et al 2001). In such cases of early-onset MDD (defined as onset prior to age 18 years), patients usually continue to suffer from episodes of MDD during adulthood as well (Birmaher et al 1996). Adolescents have a high risk of recurrence, with a 40% cumulative probability after two years and a 70% recurrence probability after five years (Thorpe et al 2001). There is no gender difference in prevalence rates prior to puberty, but MDD is more frequent in females than in males postpubertally (Fleming and Offord 1990). Early-onset MDD is similar in many ways to MDD in adults, but early-onset major depression is a particularly serious form of affective disorder due to the high recurrence rate present at a critical developmental period. Furthermore, adolescents with early-onset MDD usually develop poorly both psychosocially and academically, with an increased risk for substance abuse, switch to bipolar illness, and suicide (Birmaher et al 1996; Kovacs 1996). MDD in children and adolescents is frequently present with some form of comorbid anxiety disorder (including obsessive-compulsive disorder), disruptive behaviour disorder or substance abuse. Early-onset depression is also frequently misdiagnosed as "adjustment disorders of adolescence" or "attention deficit/hyperactivity disorder" (ADHD) (Birmaher et al 1996).

4.2.2 *Acute-phase treatment of children and adolescents with MDD*

Early detection and treatment intervention is important in ameliorating the poor outcome of early-onset depression. Antidepressants may prove useful in some cases and are especially recommended for patients with severe depression and psychosis (Birmaher et al 1998). Almost all double-blind controlled trials reported no significant difference between TCAs and placebo. A meta-analysis of 12 randomized controlled trials comparing the efficacy of orally administered tricyclic medication with placebo in depressed subjects aged six to 18 years suggested that TCAs show only moderate effects (Hazell et al 2001). Thus, the therapeutic role of TCAs (particularly desipramine and imipramine) for children and adolescents must be seriously weighed against lethality of overdose, the possibility of sudden unexplained death (possibly related to cardiac conduction problems; Wilens et al 1996), and the availability of safer and easier to monitor medications (Geller et al 1999). All but one study found a high placebo response rate of 50% to 70%, suggesting that children and adolescents are more likely than adults to respond to a placebo.

In contrast to TCAs, SSRIs appear to have superior efficacy compared to placebo in children and adolescents (Level B). In a randomized controlled comparator trial of an SSRI, fluoxetine was shown to be superior to placebo with a response rate of 56% compared to 33% with TCAs (Emslie et al 1997). In another randomized controlled trial, paroxetine, but not imipramine, had a better reponse rate (67% and 58%, respectively) than placebo (55%) (Keller et al 2001). The newer antidepressants have not yet been studied in RCTs, but small open-label studies of venlafaxine (Mandoki et al 1997) and nefazodone (Goodnick et al 2000) have shown some promising results (Level D).

In summary, although enough data from direct comparison studies with other antidepressants are missing, SSRIs seem to be the antidepressants of choice in the pharmacotherapy of children and adolescents (Level B). Unfortunately, pharmacokinetic data and systematic safety studies of SSRI use by the pediatric age group are sparse (Leonard et al 1997). While children should be treated with lower doses, the recommended SSRI dosage for adolescents is similar to that for adults. ECT may be considered for acutely suicidal, psychotic or treatment-resistant depression (Thorpe et al 2001). There is very limited data on the use of other strategies (e.g. augmentation with lithium or thyroid hormone (T_3 or T_4)) for treatment-resistant depression in individuals with early-onset depression. However, the same strategies that have been

recommended for adults may also be used for children and adolescents (Birmaher et al 1998).

The most promising psychotherapeutic interventions for depression in children are individual rather than family therapies (Birmaher et al 1998). Among the psychotherapeutic modalities, CBT and IPT are the foremost and best-evidenced approaches for treating early-onset MDD. These treatments are particularly effective for adolescents (Harrington et al 1998). A systematic review of six RCTs of CBT reported CBT to be an effective treatment for depressive symptoms and for mild, but not severe, depressive disorders (Harrington et al 1998). There is some indication that CBT may also be a useful preventive intervention, though this remains to be conclusively demonstrated. There have been no systematic RCTs comparing psychological treatments with pharmacotherapy (Thorpe et al 2001).

4.2.3 *Continuation-phase treatment of children and adolescents with MDD*

Given the high rate of relapse of depression, continuation therapy is recommended for all children and adolescents for at least six months. As with adults, antidepressants should be continued at the same dose used to attain remission of acute symptoms. At the end of the continuation phase, for patients who do not require maintenance treatment, medications should be discontinued gradually for at least six weeks. Additional psychotherapy may help patients and families to consolidate the skills learned during the acute phase, cope with the psychosocial sequelae of the depression, effectively address environmental stressors and understand inner conflicts that may trigger a depressive relapse (Birmaher et al 1998).

4.3 Treatment of depression in older adults

MDD in late life is more prevalent than previously reported. Underrecognized and undertreated, MDD in late life is also associated with a poor prognosis (Cole et al 1999; Katona 2000; Steffens et al 2000). The elderly population is perhaps the most difficult to treat effectively and safely for MDD. Changes in physiology associated with advancing age produce clinically significant differences in drug metabolism and pharmacokinetics in older patients versus younger adult patients. Older adults are also more likely than younger adult patients to receive treatment for multiple illnesses, which increases the potential for serious pharmacodynamic and pharmacokinetic drug-drug interactions (Preskorn 1993).

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 comorbidity, dementia or neurological problems (Chapter 4.4; Flint 1998; Roose and Suthers 1998). Three meta-analyses of different classes of antidepressants in older (age > 55 or ≥ 60) depressed patients did not show significant differences in antidepressant class outcomes relative to efficacy or tolerability (Mittmann et al 1997; McCusker et al 1998; Gerson et al 1999).

Nortriptyline, a secondary amine tricyclic compound, has been the most systematically studied antidepressant in the elderly. The choice has been based on better tolerability, especially relative to cardiovascular adverse events, in comparison with other tricyclic antidepressants and because of the known plasma level range (70 to 170 ng/ml) associated with efficacy (Roose and Suthers 1998). The efficacy and safety of nortriptyline for the treatment of major depression in older adults has been well established in placebo-controlled studies and in comparative trials with other antidepressants (Level A) (Flint 1998; Roose and Suthers 1998; Reynolds et al 2001). The efficacy and safety of the SSRIs in older depressed patients have been evaluated in a number of clinical trials of sertraline, paroxetine and fluoxetine (Level A) (Dunner et al 1992; Tollefson et al 1995; Roose and Suthers 1998; Mulsant et al 1999; Bondareff et al 2000). In a randomized controlled trial comparing sertraline with fluoxetine, both drugs were equally effective for the treatment of depressed older outpatients (Newhouse et al 2000). Venlafaxine and reboxetine have also been shown to be effective in comparative double-blind trials (Katona et al 1999; Staab and Evans 2000) (Level B). Additionally, a meta-analysis found efficacy for moclobemide in geriatric patients (Level A) (Angst and Stabl 1992).

Compared to young adults, response to antidepressant treatment may be slower in older adults and characterized by a higher relapse rate during continuation-phase treatment (Reynolds et al 1996). There is evidence from a placebo-controlled study of dothiepin which suggests that older patients may continue to benefit from active continuation-phase treatment for up to 12 months (Old Age Depression Interest Group 1993).

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, of which a sizable proportion of the patients were older than 60, the two drugs were equally effective for depression, but nortriptyline was associated with a significantly higher rate of serious cardiac adverse events (Roose et al 1998). Anticholinergic adverse events (e.g. cognitive impairment, constipation, urinary retention) are another important issue in the older population (Table 4). In a clinical trial with older depressed patients, nortriptyline induced five times more

serum anticholinergicity than paroxetine, as well as more anticholinergic adverse events (Pollock et al 1998).

Due to the equal efficacy of the various classes of antidepressants, choice of medication is determined by comparing side effect profiles. Because older patients are more prone to orthostatic hypotension and more sensitive to other adverse events, such as anticholinergic effects, SSRIs and the other/newer antidepressants are generally preferred over the TCAs (Level A) (Katona 2000). Older patients typically require a lower oral dose than do younger adult patients. Higher plasma concentrations for a given dose are generally found in older compared to younger individuals (Anderson et al 2000; American Psychiatric Association 2000).

4.3.1 *Treatment-resistant depression in older adults*

Treatment-resistant major depression is a common clinical problem in older depressed patients, reported to affect up to one-third of this population. Unidentified comorbid medical or psychiatric conditions and misdiagnosis often contribute to treatment resistance. Atypical depressive symptoms, such as somatic and cognitive symptoms, and comorbid medical conditions that can themselves produce depressive symptoms, often make it difficult to accurately assess antidepressant response in this age group (Mulsant and Pollock 1998; Katona 2000).

In older adult patients, as in younger adult patients, the selection of the right antidepressant, the right dose, and the right treatment duration constitute the treatment variables essential in ensuring optimal therapeutic response. Options for treatment-resistant depression in older adults involve reconsideration of the diagnosis, optimizing treatment and use of alternate therapeutic approaches, including switching to another agent, combination therapy and electroconvulsive therapy. Although there are fewer data than for young adults (see Chapter 2.1.9.4.1) that support the use of lithium augmentation, lithium seems to be an effective augmenting agent in the treatment of depression in older adults (Level C) (Kushnir 1986; Katona and Finch 1991; Zimmer et al 1991; Uehlinger et al 1995). However, the use of lithium is more problematic in older adults due to less efficient clearance and interaction with concomitant medications (Sproule et al 2000). Regular clinical examination and regular blood level monitoring, aimed at keeping serum lithium levels within the range of 0.4 to 0.8 mmol/L (mEq/L), enables most older adults to safely continue lithium treatment (Katona and Finch 1991).

ECT is an important treatment option for the treatment of depression in older adults since comorbid medical conditions, poor tolerance of psychotropic medications, and frequent psychotic features are common conditions of this age group. ECT is safe in older patients and possibly even more efficacious in the treatment of depression in the old-old (> 75 years) and young-old (60 to 74 years) than in the treatment of young adults (< 59 years) (Tew et al 1999; Manly et al 2000). ECT has been more efficacious than antidepressants, including combination and augmenting schemes, for treatment of psychotic depression in late life (Level B) (Flint and Rifat 1998).

4.4 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 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 tumours),
- 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 erythematodus),
- 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 even up to 40% to 50% in patients with neurological disorders (AHCPR 1993; Devanand et al 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 undertreatment 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, the 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, psychotherapeutic intervention seems 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 (Level A) (Gill and Hatcher 2001). The evidence was consistent across these trials, apart from two studies in cancer, where mianserin produced significantly fewer dropouts than placebo. There is 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).

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

Depressive symptoms are common in *Alzheimer's disease*, but severe depression is unusual. Four placebo-controlled trials with antidepressants have been carried out in elderly patients with depression and Alzheimer's Disease (Level A). 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 of 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 SSRIs 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 SSRIs 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 (Level C) (Zesiewicz et al 1999). In PD with comorbid depression, SSRIs (sertraline, paroxetine) or moclobemide have been recommended as first-line treatment (Allain et al 2000). However, the combination of SSRIs 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 comorbid illnesses who take nonpsychotropic medications (Chapter 2.1.8; Kent 2000).

4.5 Treatment of depression 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%), information to guide patients and physicians through a consideration of treatment during pregnancy is limited (Level C) (Wisner et al 2000; Altshuler et al 2001). Major depressive disorder occurring during pregnancy is a difficult therapeutic problem (American Psychiatric Association 2000). Three primary risks are associated with medication use during pregnancy: 1) teratogenicity; 2) perinatal syndromes (neonatal toxicity); and 3) postnatal behavioural sequelae. In contrast to mood stabilizers (lithium, carbamazepine, and valproate), which do have some teratogenicity, antidepressants (TCAs, SSRIs) do not seem to confer increased risk of organ dysgenesis (Altshuler et al 1996, 2001). TCAs and SSRIs did not increase risk of intrauterine death or major birth defects (Wisner et al 1999). Decreased birth weights of infants exposed to fluoxetine in the third trimester were identified in one study (Chambers et al 1996). The (neuro-)development of children whose mothers took TCAs or fluoxetine during gestation did not differ from that of controls (Nulman and Koren 1996; Nulman et al 1997). Direct drug effects and transient withdrawal symptoms (e.g., jitteriness, tachypnea) occurred in some infants whose mothers were treated with antidepressants near term (Wisner et al 1999). 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 following drug discontinuation (risk-benefit decision-making). Psychotherapy and ECT should be considered as important treatment alternatives. Close monitoring and interventions for patients with identified risks (e.g., poor weight gain) are recommended (Wisner et al 1999).

Following childbirth, many women are at high risk for the onset or recurrence of a mood disorder. The transient seven to 10 day depressive syndrome referred to as "postpartum blues"

typically does not meet the criteria for major depressive disorder and does not require medication (American Psychiatric Association 2000). The term "postpartum depression" refers to major depressive episode occurring within four weeks of delivery. Studies have shown a consistent incidence of depression in 10% to 15% of mothers in the early weeks after delivery (Hoffbrand et al 2001). Women with a history of MDD have a 25% to 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 (Level C) (Wisner et al 1996; Hoffbrand et al 2001; Burt et al 2001). 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. It is also important that the pediatrician is aware of the infant's exposure to psychoactive medication through the breast milk (assuming the mother consents to having that information shared). The agents most scrutinized in breast-feeding women are paroxetine, sertraline, fluoxetine, clomipramine and nortriptyline (Stowe et al 2000; Hendrick et al 2001).

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