

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 2: Maintenance Treatment of Major Depressive Disorder and Treatment of Chronic Depressive Disorders and Subthreshold Depressions

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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 the complete spectrum 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). The first part of these WFSBP guidelines on unipolar depressive disorders covered the acute and continuation treatment of major depressive disorder (Bauer et al 2002). This second part of the guidelines covers the management of the maintenance-phase treatment of

major depressive disorder, as well as the treatment of chronic and subthreshold depressive disorders (dysthymic disorder, double depression, minor depressive disorder and recurrent brief depression). These guidelines are primarily concerned with the biological treatment (including antidepressants, lithium, other psychopharmacological and hormonal medications, and electroconvulsive therapy) of young adults and also, albeit to a lesser extent, children, adolescents and older adults.

Key words: major depressive disorder, chronic depressive disorders, dysthymic disorder, subthreshold depressive disorders, maintenance treatment, evidence-based guidelines, pharmacotherapy, antidepressants, lithium, ECT.

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Table of Contents

	Executive Summary of Recommendations
1	Long-Term Treatment of Unipolar Depressive Disorders
1.1	Introduction
1.2	Goal and Target Audience of WFSBP Guidelines
1.3	Methods of Literature Research and Data Extraction
1.4	Evidence-Based Classification of Recommendations
2	Maintenance-Phase Treatment of Major Depressive Disorder
2.1	General Treatment Principles of Maintenance Treatment
2.1.1	Goals and Indications
2.1.2	Treatment Implementation
2.2	Pharmacotherapy of Maintenance Treatment
2.2.1	Evidence of Efficacy
2.2.1.1	Antidepressants
2.2.1.2	Lithium
2.2.1.3	Carbamazepine and Other Mood Stabilizers
2.2.2	Comparative Efficacy
2.2.3	Tolerability and Side Effects of Maintenance Medications
2.2.4	Treatment of Symptomatic Worsening and Recurrence
2.2.5	Maintenance Treatment Options for Prophylaxis - Resistant Depression
2.3	Duration and Discontinuation of Maintenance Treatment
2.4	Switching from Unipolar Depression to Bipolar Disorder
2.5	Electroconvulsive Therapy (ECT)
2.6	Psychotherapy
2.7	Maintenance-Phase Treatment of MDD in Special Age Groups
2.7.1	Children and Adolescents
2.7.2	Older Adults
3	Treatment of Chronic Depressive Disorders
3.1	Introduction
3.2	Dysthymic Disorder
3.2.1	Pharmacotherapy of Dysthymic Disorder
3.3	Double Depression and Other Chronic Depressions
4	Subthreshold Depressions
5	References

Tables and Figures

Table 1: Factors Associated with Increased Risk for Recurrence in Major Depressive Disorder – page 74

Figure 1: Flow Chart – Therapeutic Options for Maintenance Treatment of Major Depressive Disorder – page 75

Executive Summary of Recommendations

• General Recommendations

The long-term course of unipolar major depressive disorder (MDD) is characterized by high rates of recurrence and prolonged symptomatic chronicity. The primary goals of maintenance (prophylactic) treatment are to prevent a new episode of depression, a recurrence, suicide and development of chronicity. Consideration of the patient's course of illness and treatment history is essential for the implementation of maintenance-phase treatment. Even though no definite recommendation can be given as to when prophylactic therapy should be initiated, it is clearly indicated in situations associated with a high risk of recurrence. For patients who have had three or more episodes of major depression, and in patients with a high prior rate of recurrence (e.g., two episodes within five years), longer term maintenance therapy is indicated. Duration may vary from three years to lifetime, but in general the more adverse the prognosis, the longer the maintenance therapy. Adverse prognostic indicators for recurrence include a high number of previous episodes, residual symptoms at remission, previous longer episodes and chronicity, more severe previous episodes, onset early in life, concurrent dysthymic disorder ("double depression"), relapse after medication withdrawal, previous episode within the last year, concurrent substance abuse or anxiety disorders, and family history of major depressive disorder in first degree relatives.

Key elements of long-term treatment of MDD include 1) psychoeducation, 2) pharmacotherapy, and 3) adherence monitoring. Adjunctive depression-targeted psychotherapy may be considered in individual patients. Because maintenance treatment requires compliance with medication, education and a close therapeutic alliance with patients and their families are essential. To prepare patients and their families for maintenance treatment, they should be informed about the following topics: typical course of the illness, treatment options, medication effects and side effects, use of (daily) self-report instruments to track mood and early warning signs of relapse or recurrence, long-term perspectives, and projected end of treatment. Other principles of maintenance treatment are to distinguish between spontaneous symptomatic fluctuations ("blips") and "true" recurrences. In contrast to "blips", which are self-limited and do not require specific interventions, recurrences must be treated aggressively. It is also essential to regularly check adherence to medication and to detect breakthrough symptoms early on.

• Specific Treatment Recommendations

The medications of first choice for the maintenance treatment of MDD are either the antidepressant with which remission was achieved

in the acute and continuation phase or lithium. Many patients receive antidepressants during the acute and continuation phase, and the best treatment recommendation to prevent recurrence of depression is to continue the antidepressant medication at the same dose during the maintenance phase. Randomized placebo-controlled studies (usually conducted for one or two years during maintenance treatment) indicate that tricyclic antidepressants (TCAs), irreversible monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs) are effective in preventing recurrence of depression. Recent evidence suggests that the "newer" antidepressants have superior long-term efficacy and better tolerability compared to traditional antidepressants (e.g., TCAs). Another first choice medication for the maintenance treatment of MDD is lithium. With respect to lithium therapy, serum lithium levels of 0.5 to 0.8 mmol/L (mEq/L) determined 12 hours after the last lithium intake are usually recommended for maintenance treatment. However, the "optimal" serum lithium level may vary somewhat from patient to patient, in the range of 0.4 to 1.0 mmol/L, depending on individual effectiveness and tolerability of side effects. There is modest evidence that carbamazepine is an alternative medication in the maintenance treatment of MDD. Other mood stabilizers that are used for bipolar affective disorders (e.g., valproate [divalproex], lamotrigine or gabapentin) have not been studied in randomized controlled trials for the maintenance treatment of MDD. Periodic (maintenance) electroconvulsive therapy (ECT) has been recommended for patients who fully responded to ECT during the acute and continuation treatment phase and especially for those who are not eligible for or who do not respond to maintenance medication treatment.

The duration of continuation treatment following acute treatment should be six to nine months. Treatment length required for maintenance is not yet fully determined. However, three years of maintenance therapy is most commonly appropriate for recurrent patients, particularly when an episode prior to the present one has occurred in the last five years or when remission has been difficult to achieve. Maintenance treatment for five to 10 years, or even indefinitely, is recommended for those patients at greater risk, particularly when two or three attempts to withdraw medication have been followed by another episode within a year.

Although the amount of data from controlled studies is still limited, results clearly indicate efficacy of various antidepressants (TCAs, SSRIs and other "newer" antidepressants) for dysthymic disorder. Although the optimal length of pharmacotherapy for dysthymia has not been studied in a controlled design, a course of treatment with an antidepressant for at least two to three years is recommended, as in MDD.

Although subthreshold depressive disorders are highly prevalent in the general population and in primary care settings, controlled treatment data involving pharmacotherapy is even more sparse than for dysthymic disorder. Given the limited data from controlled studies for subthreshold depressive disorders, evidence-based treatment recommendations cannot be given at this point. However, a treatment trial with one of the well-tolerated antidepressants is worth trying in more chronic and unremitting cases.

Withdrawal of antidepressants and lithium after longer term use (e.g., longer than six months) should always be gradual, with dose reductions over at least three months. Abrupt cessation of antidepressants after longer term use can lead to withdrawal syndromes. Rapid, although not abrupt, withdrawal can lead to rebound relapse and recurrence. Where symptoms return during or after withdrawal, full-dose maintenance treatment should be initiated.

1 Long-term treatment of unipolar depressive disorders¹

1.1 Introduction

Major depressive disorder (MDD), in its classic form, presents as a recurrent disorder (Angst 1986; Judd 1997; Kiloh et al 1988). Major depressions that do not respond to treatment or that spontaneously remit will suffer subsequent relapses or recurrences. Fifty percent to 85% of the patients who have an episode will have another episode of major depression (Mueller et al 1999; Andrews 2001; American Psychiatric Association 2000). The likelihood of a recurrence increases with the number of previous depressive episodes and the severity of the current episode (Angst 1999). Patients who have had three episodes of major depression have a 90% chance of having another (NIMH Consensus Development Conference 1985). Among others, risk factors for recurrence of MDD are: prior history of multiple episodes of MDD, early age at onset, persistence of dysthymic symptoms after recovery from an episode of MDD, presence of an additional, non-mood psychiatric diagnosis, and presence of a chronic physical disorder (Kovacs et al 1997; American Psychiatric Association 2000). Factors that have been associated with increased severity of subsequent depressive episodes include a history or a prior episode complicated by serious suicide attempts, psychotic features or severe functional impairment (American Psychiatric Association 2000).

In recent years it has become apparent that the long-term course of unipolar MDD is not only characterized by high rates of recurrence but also

dominated by prolonged symptomatic chronicity (Judd 1997; Judd et al 1998). Most patients with MDD return to the premorbid level of functioning between episodes of major depression. However, in approximately 30% of the severe or hospitalized depressed patients, residual symptoms and social or occupational impairment persists. It is now well established that about one-third of patients suffering from severe major depression will have a chronic course marked by at least two years of illness (Keller et al 1986; Scott 1988; Nierenberg 2001; American Psychiatric Association 2000; Judd and Akiskal 2000). Epidemiological and prospective clinical follow-up studies have also documented that the typical course of unipolar MDD involves fluctuating symptoms in which depressive subtypes included in official diagnostic systems do not represent discrete disorders, but are stages along a dimensional continuum (spectrum) of symptomatic severity (Angst et al 2000; Judd and Akiskal 2000). The group of chronic depressive disorders encompasses four subtypes of depressive illness:

- major depressive disorder, recurrent, without full interepisodic recovery (in incomplete remission),
- major depressive disorder, currently in a chronic (duration of \geq two years) episode (chronic major depressive disorder),
- dysthymic disorder,
- "double depression" (concurrent dysthymic disorder and major depression).

The group of "subthreshold depressions" (depressive disorders not otherwise specified, NOS) includes depressive conditions in which the number, duration or quality of symptoms is insufficient to meet the DSM criteria for a diagnosis of major depression (American Psychiatric Association 1994a; Judd et al 1998; Akiskal and Cassano 1997; Angst and Merikangas 1997).

Patients with an early onset and older adults suffering an initial depressive episode after the age of 60 appear to be at greater risk for the development of chronicity (Klerman and Weissman 1989). Individuals suffering from either dysthymia alone or "double depression" have significantly greater impairment in functioning than those with major depression alone, depressive symptoms or past episodes of major depression (Wells et al 1992). Residual (subthreshold) symptoms in the course of MDD are associated with a high risk for early episode relapse and a significantly more chronic future course of illness. Asymptomatic recovery from MDD is associated with significant delays in episode relapse and recurrence and a more benign course of illness (Judd and Akiskal 2000; Judd et al 2000).

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

¹ It is emphasized that the treatment of dysthymic disorders, subthreshold depressions and other chronic depressive disorders does not involve only long-term treatment but also acute treatment. However, for editorial reasons only, both acute and long-term treatment issues are covered in Part 2 of these guidelines.

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 use of anticonvulsants in maintenance treatment, the effectiveness and positioning of lithium in the maintenance treatment of unipolar depressive disorders, and the positioning of psychotherapy in guidelines for the biological treatment of depressive disorders.

These guidelines are intended for use in clinical practice by *all* physicians seeing and treating patients with these conditions. They should be considered as guidelines only because the ultimate judgement 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, lithium, other psychopharmacological and hormonal medications, and electroconvulsive therapy) of unipolar depressive disorders in 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 are covered by separate WFSBP guidelines [Grunze et al In Press]). The management of the acute and continuation treatment of major depressive disorder was covered in Part 1 of the WFSBP guidelines (Bauer et al 2002). This second part of the guidelines covers the management of maintenance-phase treatment of major depressive disorder, as well as treatment of chronic depressive disorders and subthreshold depressive disorders. 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 follow-

ing 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 Adolescents 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 of the MEDLINE database (until August 2001); major pertinent review articles identified by a search of 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 feasibility². 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.

² 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.

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 \geq 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 \geq one prospective, moderately large (sample size of \geq 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 \geq 10 participants) showed efficacy, or at least two prospective, open-label study/case series (with a sample size of \geq 10 participants) showed efficacy.

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

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

2 Maintenance-phase treatment of major depressive disorder

2.1 General treatment principles of maintenance treatment

2.1.1 Goals and indications

The goals of long-term, maintenance (prophylactic) treatment are to prevent a new episode of depression (a recurrence), suicide and development of chronicity. A recurrence is an episode that appears after a completely asymptomatic period (remission) has been achieved for a six-month period (recovery) (Frank et al 1991;

Kupfer 1993). The consideration of the patient's course of illness and treatment history is essential for the implementation of maintenance phase therapy. Even though no definite recommendation can be given as to when prophylactic therapy should be initiated, it is clearly indicated in situations associated with a high risk of recurrence (Brunello et al 1995; Angst 1999; Dawson et al 1998; Paykel 2001) (Table 1). In addition to these risk factors, patient preference, severity of functional impairments and side effects experienced during the continuation phase also play a role in determining whether or not maintenance treatment should be implemented (AHCPR 1993; American Psychiatric Association 2000).

2.1.2 Treatment implementation

Key elements of long-term treatment of recurrent depressive disorders include 1) psychoeducation, 2) pharmacotherapy, and 3) adherence monitoring. Adjunctive depression-targeted psychotherapy may be included in some cases. Because maintenance treatment requires compliance with medication, education and a close therapeutic alliance with patients and their families are essential (Kupfer 1993). Education does not only reduce treatment attrition, but also leads to a better outcome (Rush 1999). To prepare patients and their families for maintenance treatment, they should be informed about the following topics: typical course of the illness, treatment options, medication effects and side effects, use of (daily) self-report instruments to track mood and early warning signs of relapse or recurrence, long-term perspectives, and projected end of treatment. Patients should also be instructed to inform all of their doctors about all the medications they are taking. It is also important to inform the patient that several different treatments may need to be tried before the treatment that is best for them is identified.

Other principles of maintenance treatment are to distinguish between spontaneous symptomatic fluctuations ("blips") and "true" recurrences. In contrast to "blips", which are self-limited and do not require specific interventions, recurrences must be treated aggressively. It is also important to regularly check adherence to medication and to detect breakthrough symptoms early on (Rush 1999).

Recently, a relapse prevention program (a low intensity intervention including enhanced patient education, visits with a depression specialist, telephone calls, symptom monitoring) for depressed patients in primary care significantly improved antidepressant adherence and depressive symptoms outcome in a randomized controlled 12-month trial compared with usual primary care (Katon et al 2001).

The frequency of visits may range from monthly visits to every three to six months in stable

Table 1

Factors associated with increased risk for recurrence in major depressive disorder

- three or more episodes of major depression
- high prior rate of recurrence (e.g., two episodes within five years)
- previous episode in the last year
- residual symptoms during continuation phase treatment
- residual subsyndromal symptoms at remission
- concurrent dysthymic disorder ("double depression")
- severity of episodes (includes suicidality and psychotic features)
- longer previous episodes
- relapse after medication withdrawal
- concurrent coexisting substance abuse
- concurrent coexisting anxiety disorders
- family history of major depressive disorder in first degree relatives
- onset prior to age 30

patients for (brief) psychiatric evaluation and medication monitoring (e.g., side effect assessment, medication blood levels). In unstable patients, more frequent visits are required. If the patient develops a medical condition while on maintenance treatment, potential drug-drug interactions should be considered. Patients/families should also be instructed to inform the treating physician if and when signs of depression reoccur.

2.2 Pharmacotherapy of maintenance treatment

2.2.1 Evidence of efficacy

Pharmacotherapy is the most studied treatment modality in the long-term maintenance treatment of recurrent unipolar depression. Among the therapeutic options available, antidepressants and lithium have received the most study. The majority of controlled trials investigating these medications in maintenance treatment demonstrated efficacy for relapse prevention (Level A) (Solomon and Bauer 1993; AHCP 1993, 1999; Davis et al 1999).

The medications of first choice for maintenance treatment in unipolar depression are either the antidepressant with which remission was achieved in the acute/continuation phase or lithium (NIMH Consensus Development Conference 1985; AHCP 1993; Prien and Kocsis 1995; American Psychiatric Association 2000; Paykel 2001). Likely reasons why antidepressants may be preferred to lithium as prophylactic agents are that patients are usually treated with antidepressants during the acute/continuation phase and that patients usually prefer to use medication that does not require regular monitoring by blood tests (Figure 1). The final choice of prophylactic agent must depend on how individual patients respond to and tolerate treatment with antidepressants and lithium (Schou 1997). A patient's preference and their own or their family member's experience with maintenance treatment should also be considered in the choice of the medication.

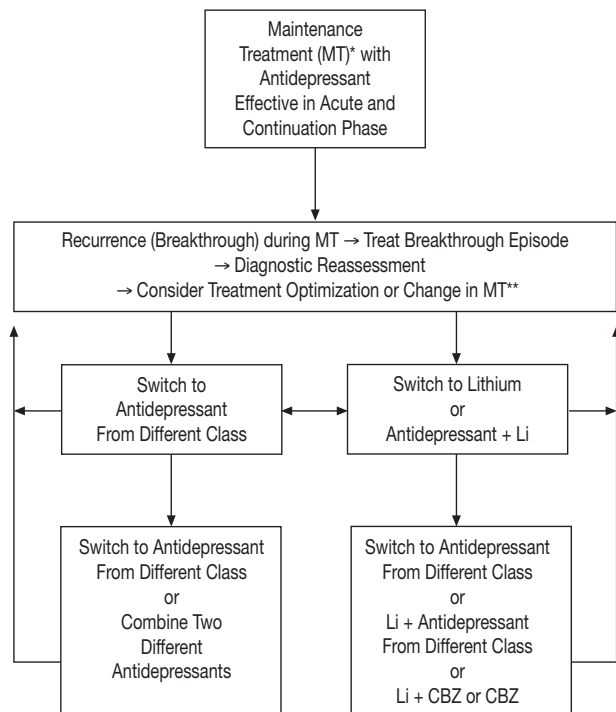
2.2.1.1 Antidepressants

Many patients receive antidepressants during the acute and continuation phase, and the best treatment recommendation to prevent recurrence of depression is to continue the antidepressant medication that was effective during the acute and continuation phase of treatment at the same dose during the maintenance phase (Level B) (Frank et al 1993; Franchini et al 1998). In these two latter studies, the group of patients who received only half of the acute-phase dose of imipramine (Frank et al 1993) or paroxetine (Franchini et al 1998), rather than the full dose, showed a significantly higher recurrence rate. Randomized placebo-controlled studies (usually for one or two years during the maintenance phase) of antidepressants in the prophylactic treatment of depression indicate that TCAs

(amitriptyline, imipramine, nortriptyline, maprotiline) (Level A), MAOIs (phenelzine) (Level A) (Solomon and Bauer 1993; Montgomery 1994; AHCP 1993, 1999; American Psychiatric Association 2000; Paykel 2001) and SSRIs (Level A) (citalopram [Hochstrasser et al 2001], fluoxetine [Gilaberte et al 2001], fluvoxamine [Terra and Montgomery 1998] and paroxetine [Montgomery and Dunbar 1993]) are effective in preventing recurrence of depression.

2.2.1.2 Lithium

The use of lithium as a maintenance therapy for unipolar recurrent depression is well established (Level A) (Goodwin and Jamison 1990; Schou 1997; Dunner 1998; Coppen 2000; Paykel 2001). Two meta-analyses found evidence that lithium is more effective than placebo in preventing recurrence of unipolar depressive illness (Souza and Goodwin 1991; Burgess et al 2001), whereby the results were statistically significant in only one of these two studies (Souza and Goodwin 1991). Over the past decade, evidence has accumulated from retrospective and prospective studies that long-term lithium prophylaxis may reduce suicide risk and even normalize the high mortality rate (Level C) (Coppen et al 1990; Müller-Oerlinghausen 1992, 1994; Tondo et al 1997; Schou 2000). A randomized 2.5-year



Abbreviations: CBZ = carbamazepine, MT = maintenance treatment, Li = lithium;
 * Maintenance electroconvulsive therapy (ECT) is an option for patients responding to ECT in the acute-phase treatment or who fail to respond to two or more maintenance medication treatments
 ** Additional course of psychotherapy may also be considered.

Figure 1
 Flow chart - Therapeutic options for maintenance treatment of major depressive disorder

maintenance treatment study in patients with major affective disorder showed significantly fewer suicides and suicide attempts in the lithium group compared with the carbamazepine group (Thies-Flechtner et al 1996). Furthermore, clinical findings suggest that the anti-suicidal property of lithium acts independently of its "classical" episode preventive effect (Schou 1997; Bocchetta et al 1998; Grof 1998). However, a meta-analysis found no definitive evidence as to whether lithium has an anti-suicidal effect since a small number of deaths and suicides, and the absence of suicidal behaviour, were present in the data analyzed (Burgess et al 2001).

Serum lithium levels of 0.5 to 0.8 mmol/L (mEq/L) drawn 12 hours after the last lithium intake are usually recommended for maintenance treatment (Schou 1989). However, the "optimal" serum lithium level may vary somewhat from patient to patient, in the range of 0.4 to 1.0 mmol/L, depending on individual effectiveness and tolerability of side effects (Schou 1989; Birch et al 1993). These recommended serum lithium levels are usually achieved with a daily dose of 800 or 900 mg (dosage varies depending on availability of lithium tablets) to 1200 or 1500 mg lithium carbonate (600 mg to 1000 mg for Asian patients) in patients 60 years of age or younger, or 400/450 mg to 800/900 mg lithium carbonate in older patients (Birch et al 1993). It is irrelevant for efficacy whether lithium tablets are administered once or twice daily. Some patients find that a single daily dose facilitates long-term treatment compliance and reduces side effects. In general, extended release forms of lithium are better tolerated.

2.2.1.3 Carbamazepine and other mood stabilizers

Among the group of mood stabilizer medications that are used for the treatment of bipolar disorder, the most studied agent in open and comparator studies other than lithium is carbamazepine (Level C). Carbamazepine has been studied in small double-blind comparator trials with lithium in recurrent major depression (for more information on study results see Chapter 2.2.2 below) (Placidi et al 1986; Simhandl et al 1993). Recommended serum levels of 4 to 12 µg/ml (17 to 50 µmol/L), measured 12 hours after the last drug intake (and not sooner than five days after the last change in dosage unless toxicity is suspected), relate more to anticonvulsant activity than to mood stabilizing efficacy of recurrent affective disorders. However, serum carbamazepine levels can serve as guidelines for medication compliance and excessive adverse effects (Bezchlibnyk-Butler and Jeffries 1996). Maintenance doses average about 800-1600 mg/d, but may be lower in routine clinical practice. Because carbamazepine can induce its own hepatic metabolism (via cytochrome CYP450 isoenzymes), determinations of serum carbamazepine should be performed every

second week for the first two months after initial treatment, every second month for the next six months, and then at clinical discretion thereafter, or when there is a major change in the dosage or drug regimen. Induction of CYP3A4 by carbamazepine will also accelerate phase I reactions of drugs that are used in addition to carbamazepine, if they are metabolized via CYP3A4 (Spina et al 1996). If dose adaptation of concomitant drugs is also necessary, monitoring of drug concentrations in the serum can be useful.

Other mood stabilizers (e.g., valproate [divalproex], lamotrigine or gabapentin) have not been studied in placebo-controlled or double-blind comparator trials for the maintenance treatment of unipolar depression (Davis et al 1999).

2.2.2 Comparative efficacy

A relatively small number of studies have directly compared different medications for maintenance treatment in recurrent unipolar depression (Solomon and Bauer 1993). A meta-analysis of studies comparing lithium with other antidepressants showed no conclusive advantage for lithium in the prophylaxis of unipolar illness (Souza and Goodwin 1991). In one relatively small randomized, placebo-controlled, two-year maintenance study, lithium (serum level 0.8-1.2 mmol/L) was superior to imipramine (100-150 mg/day); the combination of lithium and imipramine was not superior to lithium alone (Kane et al 1982). Another, larger randomized, placebo-controlled, two-year study reported better maintenance effects for imipramine (the mean daily dosage at the start of the maintenance phase was 137 mg, range 75-150 mg/day) than lithium (the mean serum lithium level at the start of the maintenance phase was 0.66 mmol/L, range 0.43-1.05 mmol/L) (Prien et al 1984). In the latter study, the combination of imipramine and lithium was not more advantageous than imipramine alone in preventing depressive recurrences. However, in a later reanalysis of the data, the same authors concluded that the results of the latter study could be accounted for by alternative explanations that are a consequence of the study design (Greenhouse et al 1991). One randomized, prospective, open 2.5-year trial comparing lithium (average serum lithium level 0.59 mmol/L) with amitriptyline (average dosage 98 mg/day) found significantly better prophylactic efficacy for lithium (Greil et al 1996a).

A randomized, three-year maintenance study in a group of patients with major affective disorder showed equal efficacy for lithium and carbamazepine (Placidi et al 1986); for these two medications, similar results were obtained in a randomized two-year study of unipolar depression (Simhandl et al 1993). Although the evidence for prophylactic efficacy of carbamazepine in unipolar depression is limited, results

indicate that carbamazepine may be an alternative for those patients who do not tolerate or respond to maintenance treatment with lithium or antidepressants (Level C) (Figure 1).

In the largest and probably most influential study on the use of antidepressants in maintenance treatment, a randomized three-year placebo-controlled trial, survival analysis showed full-dose imipramine (mean dose at randomization 215 mg/day) with or without Interpersonal Therapy (IPT; weekly for 12 weeks, then bi-weekly for eight weeks, and then monthly) to be the best maintenance treatment, followed by IPT with or without placebo, and then placebo (Frank et al 1990). In this study of highly recurrent unipolar depression, all patients enrolled in the three-year study had remitted on the combination of imipramine and IPT, and all had remained well for four months of continuation therapy prior to randomization. A subsequent additional two-year placebo-controlled study of the patients who completed the three-year study (Frank et al 1990) showed that imipramine (average dose of 200 mg/day) was significantly better than placebo in preventing recurrence (Kupfer et al 1992).

A number of more recent studies suggest that the "newer" antidepressants (see Part 1 of these guidelines [Bauer et al 2002]) have superior long-term efficacy and better tolerability compared with traditional TCAs (Level B) (Montgomery 1999). A randomized, placebo-controlled, two-year study comparing the efficacy of mirtazapine with that of amitriptyline found that the time to relapse was significantly longer in the mirtazapine group (Montgomery et al 1998). Similarly, a double-blind one-year study reported significantly greater improvement in some of the outcome measures in the venlafaxine group compared with imipramine (Shrivastava et al 1994).

2.2.3 Tolerability and side effects of maintenance medications

The long-term side effects and tolerability of medications are key considerations in maximizing adherence to treatment. Side effects should be as minimal as possible. Even mild to moderate side effects during maintenance treatment may lead to noncompliance, with the consequence of symptom worsening and increased risk of recurrence. Using medications with a more favourable side effect profile than the TCAs may facilitate patient compliance with pharmacotherapy, as long as these agents are effective in the maintenance treatment of depression. The "newer" antidepressants are associated with fewer long-term side effects than the older tricyclics and tetracyclics (for details about side effects of antidepressants see: Part 1 of these guidelines [Bauer et al 2002]; Peretti et al 2000; AHCP 1993, 1999; American Psychiatric Association 2000).

One advantage of maintenance therapy with *lithium* is the long experience with this agent worldwide, making the risks of long-term treatment more clear. Specialized Lithium Clinics for the prophylactic long-term treatment of patients with affective disorders have been established for more than 30 years in many countries and have provided longitudinal assessments of the side effects of lithium treatment (Schou 1997).

During the long-term use of lithium, regular laboratory monitoring of the serum lithium level (performed once to four times per year, and more frequently if clinically required, e.g., in the early stages of treatment, with older patients or after clinical changes have become apparent), thyroid function (e.g., TSH level) and renal function (creatinine) (e.g., once or twice a year) is recommended (Birch et al 1993; American Psychiatric Association 1994b; Schou 1997; Kleiner et al 1999). The purpose of measuring serum lithium levels is to ensure that high serum lithium levels are detected and lowered, and to ensure that steps are taken to prevent recurrence in case of abnormally low serum lithium levels. It is also important to educate patients and their families about the warning signs of lithium toxicity. Among the common side effects of lithium treatment are the development of hypothyroidism and goitre resulting from the interference of lithium with the synthesis and release of thyroid hormones from the thyroid gland (Lazarus 1998). The prevalence of overt ("clinical") hypothyroidism has been reported to be between 8% and 10% in patients taking lithium, compared to a prevalence of 0.5% to 1.8% reported in the general population (Kleiner et al 1999). Even higher rates have been estimated for the prevalence of subclinical hypothyroidism (in 23% of patients on lithium therapy compared to rates of up to 10.4% in the general population) (Kleiner et al 1999).

In the past, many concerns have been raised about whether long-term lithium exposure may cause irreversible kidney damage. A recent comprehensive review stated that in the vast majority of patients, the tubular damage is not associated with significant changes in glomerular filtration rate (Gitlin 1999). Clinically important glomerular dysfunction resulting from lithium treatment is rare and is unrelated to the duration of lithium therapy (Schou 1997; Gitlin 1999). A small percentage of patients treated with lithium may develop rising creatinine concentrations after 10 years or more of treatment. However, in patients treated with lithium for 15 years or more, affection of both glomerular and tubular function seems to be more common (Bendz et al 1994).

Side effects of lithium treatment are usually dose dependent and can often be prevented or relieved by a moderate reduction in dosage

(American Psychiatric Association 1994b). Side effects may include: hand tremor (counteracted by a β -blocker), goitre and hypothyroidism (additional administration of L-thyroxine [L-T₄] to achieve euthyroid status), lowered renal concentrating ability and polyuria and/or polydipsia (warning against dehydration, possibly reduction of dosage), weight gain (moderate dieting and exercise), gastrointestinal problems (e.g., nausea, dyspepsia, loose stools; managed by administering lithium with meals, switching lithium preparations or dose reduction) and, rarely, memory impairment/mental slowness (dose reduction) (Birch et al 1993; American Psychiatric Association 1994b). The most difficult side effect to treat is polyuria, which may persist in rare cases. Management includes ensuring that the lithium dose is as low as possible, switching to another lithium formula, switching to a single daily dose or changing the time of day when the medication is taken. In severe cases of lithium-induced polyuria, treatment with amiloride, a potassium-sparing diuretic or a thiazide diuretic may be tried (*Cave*: risk of thiazide-induced hypokalemia) (Jefferson et al 1987).

The most common side effects of *carbamazepine* include neurological symptoms (e.g., diplopia, blurred vision, fatigue, ataxia; usually dose-related, often transient and reversible with dosage reduction), skin rashes, mild leukopenia and thrombocytopenia (both usually reversible with dose reduction; they may reverse spontaneously with continued treatment, however, close monitoring is required), mild liver enzyme elevations and hyponatremia (American Psychiatric Association 1994b). Monitoring of laboratory values (blood count, liver enzymes, electrolytes) is recommended two to four times per year during maintenance treatment (Greil et al 1996b). Rare, idiosyncratic but potentially fatal side effects of carbamazepine (occurring usually in the first six months of treatment) include agranulocytosis, aplastic anaemia, hepatic failure, exfoliative dermatitis (e.g., Stevens-Johnson Syndrome) and pancreatitis (American Psychiatric Association 1994b). Because these idiosyncratic fatal side effects occur very rapidly, education of the patient about the signs and symptoms of hepatic, haematological or dermatological reactions, and instructions to report symptoms if they occur, are essential for treatment with carbamazepine.

2.2.4 Treatment of symptomatic worsening and recurrence

Brief, mild depressive symptoms ("blips") frequently occur during maintenance treatment. They are self-limited and, in contrast to recurrences (breakthrough episodes), do not require specific interventions or a change in the maintenance treatment plan. Psychiatric management (e.g., including dose adjustment, reassurance) and additional short-term treatment with a benzodiazepine or hypnotic medication to treat

insomnia and/or anxiety, or an adjunctive course of psychotherapy to help address specific psychosocial stressors or stressful life events, may be useful (Rush 1999).

Many patients have a somewhat predictable pattern of symptoms that appear during a prodromal phase of a full-blown recurrence. When a patient suffers a recurrence of a depressive episode despite ongoing maintenance treatment (breakthrough episode), physicians face a considerable challenge. Early intervention can shorten the length of the episode (Kupfer et al 1989). The "differential diagnosis" of a recurrence includes evaluation of occult substance abuse, occult physical illness (e.g., thyroid dysfunction), nonadherence to medication, and the possibility of adverse life events (Rush 1999). Patients experiencing a new depressive episode while taking a mood stabilizer or an antidepressant may benefit from treatment optimization (e.g., increase of serum level to the upper end of the therapeutic level, addition of thyroid hormone if thyroid function is low [particularly in lithium-treated patients], additional psychotherapeutic interventions and visits). If the patient does not improve with treatment optimization, another round of adequate acute phase treatment should be initiated followed by continuation treatment (see Part 1 of these guidelines [Bauer et al 2002]). The treatment plan for subsequent maintenance therapy should be reevaluated and a switch in the choice of the prophylactic medication should be considered (Figure 1).

2.2.5 Maintenance treatment options for prophylaxis-resistant depression

There is growing recognition that prophylactic treatment of affective disorders may be inadequate in a substantial proportion of patients. The maintenance treatment of patients with recurrent depression who experience recurrences during prophylactic treatment with standard agents, e.g. lithium or antidepressants, is one of the most challenging issues in the treatment of these disorders. However, little data from formal studies is available to guide physicians in the maintenance treatment of patients suffering from recurrences during standard prophylactic treatment (Bauer and Helmchen 2000). An algorithm including some options for the maintenance treatment of patients with MDD is presented in Figure 1. Combining an antidepressant with lithium, or combining lithium with carbamazepine, or combining two different antidepressants, are among the possible options. Adjunctive treatment with thyroid hormone (L-thyroxine) in supraphysiological doses has also been suggested for maintenance treatment of patients with prophylaxis-resistant depression (Bauer et al 2001). However, it should be emphasized that evidence of the efficacy of these combinations and of thyroid augmentation is limited (Level D).

2.3 Duration and discontinuation of maintenance treatment

The optimal moment to discontinue a long-term medication is difficult to predict. Current evidence suggests that maintenance treatment should be continued as long as the risk of recurrence persists (Brunello et al 1995). That risk is often difficult to assess in the individual patient, particularly after a long period (years) of absence of symptoms/recurrence. It appears that the likelihood of a recurrence increases with the number of previous depressive episodes (Angst 1999). However, some authors have argued that there is a similar risk of recurrence whether medication is discontinued after months or years of pharmacotherapy (Thase 1999). There is good evidence from a controlled five-year study that patients who benefit the most from continued prophylaxis are those who receive active full-dose medication for at least five years (Level C) (Kupfer et al 1992). Thus, for some patients, maintenance treatment is required for very long periods (e.g., a decade), and for others it is required indefinitely (Rush and Kupfer 2001). Three years maintenance therapy is appropriate almost as a routine for recurrent patients, particularly where an episode prior to the present one has occurred in the last five years or where remission has been difficult to achieve. Maintenance for five years or indefinitely is recommended for those patients at greater risk, particularly where two or three attempts to withdraw medication have been followed by another episode within a year.

Regardless of the reason for discontinuation, after long-term pharmacotherapy the patient should be educated about the risk of recurrence and its early warning signs. Three phenomena that may occur after discontinuing long-term antidepressant medications need to be distinguished: *recurrence* of episode (return of the original symptoms), *rebound* (return of original symptoms but with greater intensity; typically occurs if lithium or antidepressants are withdrawn too rapidly), and *withdrawal* (development of different symptoms related to drug stoppage; typically occurs if TCAs and SSRIs are abruptly stopped) (Paykel 2001). In clinical practice, antidepressants should always be withdrawn slowly after maintenance therapy. A tapering period of four to six months is recommended in long-term treated patients to allow the early detection of emerging symptoms and to minimize the risk of antidepressant medication discontinuation syndromes. During the period of discontinuation, the patient should be monitored more closely. And after the discontinuation is complete the monitoring should continue during the next couple of months (e.g., particularly for the next six months, which appear to be a period of high risk for recurrence; Rush and Kupfer 2001) to identify those in whom a relapse is likely. If the full depressive episode recurs during or after discontinuation, a

full therapeutic dosage should be readministered promptly (AHCPR 1993).

Antidepressant discontinuation syndromes have received little systematic study. Thus, most of the recommendations in the literature and in these guidelines are based on anecdotal data or expert opinion. It is agreed that a common feature of antidepressant discontinuation syndromes is the onset of symptoms within a few days of stopping the antidepressant or, less commonly, within a few days of reducing the dosage (Haddad 2001). Discontinuation symptoms are more likely to occur when abruptly stopping the dosage. They have been described with all classes of antidepressants, including TCAs (particularly those with anticholinergic and serotonergic potency), irreversible MAOIs, SSRIs and venlafaxine (Lejoyeux and Ades 1997; Edwards and Anderson 1999). Data from a randomized controlled trial (RCT) showed that discontinuation symptoms are more common with a shorter-acting SSRI, such as paroxetine, than with a longer-acting agent, such as fluoxetine (Rosenbaum et al 1998). Withdrawal phenomena (e.g., dizziness, balance and sensory disturbance, nausea or emesis, fatigue, headache, gait instability, irritability, vertigo or feeling faint, and insomnia) differ in pattern from those of depressive recurrence. Withdrawal is usually mild but may be serious for the irreversible MAOIs. Typically these symptoms subside with the reinstatement of the original drug (Haddad 2001). Although not supported by controlled data, discontinuation reactions appear less frequently in shorter courses of treatment (Anderson et al 2000).

2.4 Switching from unipolar depression to bipolar disorder

A change of diagnosis over time from unipolar depression to bipolar disorder has been described in approximately 10% to 20% of patients (Angst et al 1978; Akiskal et al 1995; Solomon et al 1997). Antidepressants, particularly TCAs, precipitate mania in some patients with apparent unipolar depression (Altshuler et al 1995). Early age at onset of MDD, greater acuteness, pleomorphic psychopathology and high rates of substance abuse have been identified as clinical predictors of the switch to hypomania (Akiskal et al 1995). If a switch to mania occurs during the maintenance phase treatment in unipolar depression, rapid tapering of the antidepressant and concomitant treatment of the manic episode is essential (for more information on the treatment of bipolar disorder, see WFSBP Guidelines for the Treatment of Bipolar Disorder [Grunze et al In Press]).

2.5 Electroconvulsive therapy (ECT)

Case reports and case series have reported on the successful use of ECT in the maintenance phase of treatment (Level D) (Nobler and Sackeim 2000). Periodic (maintenance) ECT has been re-

commended for patients who fully responded during the acute treatment phase, and especially for those who are not eligible for or who fail to respond to maintenance medication treatment. Usually, about one or two ECT treatments per month is recommended. Due to the lack of controlled and well-defined outcome studies, the long-term risks of maintenance ECT studies are unknown.

2.6 Psychotherapy

Similar to Part 1 (Bauer et al 2002), these guidelines focus on biological (somatic) treatments. Therefore, psychotherapeutic treatments alone or in combination with pharmacotherapy will only be mentioned briefly and no levels of evidence will be provided. Instead, references for further reading are given.

Although maintenance psychotherapy as the sole treatment to prevent recurrence is less studied, and at this point not recommended as a first-line treatment unless the patient does not wish to or cannot take medication for some reason (e.g., pregnancy) (AHCPR 1993), it is a treatment option for some patients. Preliminary data suggest that cognitive behavioural therapy (CBT) may be an effective treatment for preventing recurrence in patients with recurrent major depression (Teasdale et al 2000; Jarrett et al 2001), including patients who have been successfully treated with antidepressant drugs (Fava et al 1998). There is some indication that patients with residual depression benefit from CBT for preventing recurrence (Fava et al 1998; Paykel et al 1999). Maintenance interpersonal psychotherapy (IPT-M) has also been suggested by others (Frank et al 2000).

The effectiveness of combined antidepressant medication and psychotherapy has not been well studied in the maintenance phase. Some studies have failed to find the combination to be superior to either treatment modality alone in patients with mild to moderate depression (American Psychiatric Association 2000). If psychotherapy, e.g., cognitive behavioural therapy or interpersonal therapy, is combined with medication, maintenance phase treatment usually involves a decreased frequency of psychotherapeutic sessions compared to the acute and continuation phase (e.g., once a month).

2.7 Maintenance-phase treatment of MDD in special age groups

2.7.1 Children and adolescents

The American Academy of Child and Adolescent Psychiatry (1998) emphasized that there are no published data from RCTs regarding maintenance treatment of children and adolescents with MDD. Because the clinical presentations, sequelae and natural course of depression in youths are similar to those of depression in adults, the general guidelines for treatment of adults also apply to the treatment of adolescents

(American Academy of Child and Adolescent Psychiatry 1998).

2.7.2 Older adults

The efficacy and safety of nortriptyline in preventing recurrence of major depressive episodes in patients older than 59 were well determined in a three-year placebo-controlled maintenance study of nortriptyline combined with psychotherapy and nortriptyline monotherapy (Reynolds et al 1999a). Other controlled studies have also supported the efficacy of nortriptyline in preventing recurrence of major depressive episodes in older adults (Level A) (Georgotas et al 1989; Reynolds et al 1999b). Nortriptyline has been well tolerated in long-term maintenance studies of older adults. Except for a consistent increase in heart rate and dry mouth, no other adverse events were detected in comparison with placebo (Marraccini et al 1999). A similar robust maintenance effect was found with the MAOI phenelzine in a placebo RCT in older adults (Level C) (Georgotas et al 1989).

The SSRIs are being studied as alternatives for nortriptyline in the maintenance treatment of recurrent depression in older adults (Reynolds et al 2001). In an open, 18-month study, paroxetine has been shown to be comparable to nortriptyline in preventing recurrences of depression in older adults (Level C) (Bump et al 2001).

3 Treatment of chronic depressive disorders

3.1 Introduction

Undertreatment and social impairment are the most striking characteristics of chronic depressive disorders. Patients with chronic depression are often not treated, or treated inadequately (Keller et al 1995a). It has been estimated that the response rates for chronically depressed patients are equal to or slightly lower (40% to 55%) than those of nonchronic populations (Howland 1991), and relatively low placebo response rates have been reported in these patients (Rush and Thase 1997). When symptomatic improvement occurs with pharmacotherapy in chronic depression, it is associated with functional restoration (Miller et al 1998). This all indicates that patients with chronic depression may well benefit from medication treatment. There is also evidence from a controlled study that patients with major depression who have residual symptoms may improve with cognitive behavioural treatment (Fava et al 1994). Another study of patients with chronic depression found that patients with a combination of CBT and nefazodone were more likely to have a favourable response than patients with either treatment alone (Keller et al 2000).

3.2 Dysthymic disorder

ICD-10 defines dysthymia broadly as a chronic depression of mood that does not currently fulfil

the criteria for recurrent depressive disorder in terms of either severity or duration of individual episodes (WHO 1991). Similarly, DSM-IV characterizes dysthymic disorder as a chronic mild depressive syndrome that has been present for two years or longer (American Psychiatric Association 1994a). Individuals with dysthymia frequently have a superimposed major depressive disorder ("double depression") (see Chapter 3.3). Patients with "double depression" are less likely to have a complete recovery than are patients with major depressive disorder without dysthymia (American Psychiatric Association 2000). However, patients with "double depression" who are treated during a major depressive episode also benefit with respect to their dysthymia (Akiskal 1994).

Dysthymia is a relatively common disorder with a median point prevalence of 2.1% across studies worldwide (Wittchen 2000). The lifetime prevalence has been estimated to be between 3.1% (Weissman et al 1988) and 6.4% (Kessler et al 1994). There is epidemiological evidence of high comorbidity (75%) with other psychiatric disorders, mostly major depression, anxiety disorders and substance abuse.

3.2.1 Pharmacotherapy of dysthymic disorder

Traditionally, dysthymic disorder has not been the focus of pharmacotherapeutic interventions, given the chronicity and presumed nonbiological personality variables associated with it (Howland 1991). Psychotherapy and psychoanalysis were generally considered the treatment options of first choice, although these treatment modalities were not well studied in controlled designs. However, as a result of a series of placebo-controlled medication trials, this attitude has recently been changing (Shergill and Katona 2000).

Among the antidepressants found to be superior to placebo were desipramine (Kocsis et al 1996; Miller et al 2001), fluoxetine (Hellerstein et al 1993), moclobemide (Versiani et al 1997), imipramine and sertraline (Thase et al 1996; Keller et al 1998b). In a double-blind study comparing phenelzine with imipramine, the MAOI was more effective (Vallejo et al 1987). Although the amount of data from controlled studies is still limited, a comprehensive review has confirmed the efficacy of various antidepressants in dysthymic disorder (Level A) (World Psychiatric Association Dysthymia Working Group 1995). A recent meta-analysis of 15 randomized controlled trials that used various drugs (mostly antidepressants, TCAs, SSRIs and MAOIs) versus placebo in the treatment of dysthymia showed that drugs are more effective than placebo, with no difference between and within classes of drugs (Lima and Moncrieff 2001).

Although the optimal length of pharmacotherapy in dysthymia has not been studied in a

controlled design, a course of treatment with an antidepressant for at least two to three years is recommended. Patients treated with TCAs were more likely to report adverse events compared with those treated with placebo in placebo-controlled trials (Lima and Moncrieff 2001). Results of a randomized, double-blind study of sertraline and imipramine indicated that patients suffering from chronic major depression (i.e., unremitting major depression for at least two years or dysthymia with a concurrent major depression) can achieve a good therapeutic response with acute pharmacotherapy (Keller et al 1998a). In this study, both antidepressants were equal in overall efficacy, but sertraline was better tolerated. Thus, superior tolerability and better side effect profiles compared to the "older" antidepressants, e.g., TCAs, make the SSRIs and other "newer" antidepressants the prime candidates for the long-term treatment of dysthymia (Level A).

Recommended doses for dysthymia are similar to those given for acute treatment of a major depressive episode. No systematic research has been undertaken to study treatment options for patients with dysthymia who do not respond to an adequate first trial. Under such circumstances, switching to an antidepressant of a different class seems to be an appropriate option.

Geriatric dysthymia is an understudied condition (Kocsis 1998). In one placebo-controlled study, paroxetine showed moderate efficacy in reducing depressive symptoms in geriatric dysthymia (Williams et al 2000).

3.3. "Double depression" and other chronic depressions

It has been estimated that chronic depressive disorders account for 30% to 35% of all cases of depression (Kessler et al 1994). As many as 25% of patients with major depression have coexisting dysthymia, and more than 50% of the patients with dysthymic disorder will develop a major depressive episode at some point in time after the onset of their dysthymia ("double depression") (Keller and Shapiro 1982; Keller et al 1995b). Patients with "double depression" have a particularly chronic and severe course of illness. In a study comparing outpatients with "double depression" to outpatients with episodic major depression, patients with "double depression" exhibited significantly greater impairment, more severe depressive symptoms, greater comorbidity, more personality disturbance, lower levels of social support, more chronic strains, and higher rates of bipolar II and nonbipolar affective disorders in first-degree relatives (Klein et al 1988). In addition, patients with "double depression" are significantly less likely to fully recover.

Recent randomized controlled trials have shown several medications (desipramine, Kocsis et al 1996; imipramine and sertraline, Keller et al

1998a; nefadozone, Keller et al 2000) to be efficacious in the treatment of chronic depression, including "double depression" (Level A). The basic principles of treatment for chronic depression involve adequate acute-phase medication dosing for an appropriate length of time. Once full remission is achieved, the continuation and maintenance of pharmacotherapy lowers the risk of relapse and recurrence (Kocsis et al 1996; Nierenberg 2001; Trivedi and Kleiber 2001). There is evidence that patients with chronic depression particularly benefit from a combination of pharmacotherapy and psychotherapy, as seen in the combination of nefadozone and cognitive behavioural analysis system of psychotherapy (CBASP) (Keller et al 2000).

4 Subthreshold depressions

During the last decade, there has been growing interest in understanding the importance of depressive symptoms that do not reach the threshold for major depressive disorder (Angst and Ernst 1993; Sherbourne et al 1994; Pini et al 1999; Angst et al 2000; Geiselmann and Bauer 2000; Sadek and Bona 2000). The term "subthreshold depression" is now generally defined as a patient who suffers from a cluster of depressive symptoms, of which the number, duration or quality is insufficient to meet the DSM criteria for a diagnosis of major depression (Sadek and Bona 2000). Subthreshold depression includes those patients who meet criteria for *minor depressive disorder (MinD)*, *recurrent brief depressive disorder (RBD)* (Angst and Hochstrasser 1994) and *subsyndromal symptomatic depression (SSD)* (Judd et al 1994). In DSM-IV, these disorders fall under the category of depressive disorders not otherwise specified (NOS). The essential feature of MinD is one or more period of depressive symptoms that is identical to major depressive episodes in duration, but that involves fewer symptoms and less impairment (DSM-IV, American Psychiatric Association 1994a). Individuals whose presentation meets the criteria for minor depressive disorder would be diagnosed as having "adjustment disorder with depressed mood" if the depressive symptoms occur within three months of the onset of a psychological stressor (DSM-IV). In RBD, the number and severity of symptoms are identical to those in major depressive episodes and last at least two days, but less than two weeks. Judd et al (1994) defined subsyndromal symptomatic depression (SSD) as the simultaneous presence of any two or more symptoms of depression, but excluding anhedonia and depressed mood, which are present for most or all of the time, and are at least two weeks in duration. These symptoms are associated with evidence of social dysfunction occurring in individuals who do not meet criteria for diagnoses of minor depression, major depression, and/or dysthymia.

It should be emphasized that these subthreshold depressive disorders are highly prevalent in the

general population and in primary care settings, thus having a substantial impact on the mental health system (Sherbourne et al 1994; Judd et al 1994, 1996).

Controlled treatment data involving pharmacotherapy of these disorders is sparse. The majority of published studies are case reports, open label studies or retrospective analyses (Rapaport and Judd 1998; Stamenkovic et al 1998; Pini et al 1999). In one RCT of patients with *recurrent brief depression*, fluoxetine was not superior to placebo in preventing recurrences (Montgomery et al 1994). However, in an open-label study of fluoxetine, the frequency of recurrences was significantly lower (Stamenkovic et al 2001). In an RCT of *minor depression*, paroxetine showed higher response rates compared with maprotiline, but no placebo-comparison was included (Szegei et al 1997). In an RCT in older adults with *minor depression*, paroxetine improved depressive symptoms to a greater degree and more rapidly than placebo plus clinical management (Williams et al 2000).

Given the limited data from controlled studies for subthreshold depressive disorders, evidence-based treatment recommendations cannot be given at this point. Close monitoring and problem-solving therapy for recent onset cases may be useful, and a treatment trial with one of the well-tolerated antidepressants is worth trying in more chronic and unremitting cases. RCTs of antidepressants in well-defined populations are warranted. The same is true for the treatment of adjustment disorder with depressed mood (Jones et al 1999).

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