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GUIDELINES

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders. Part 2: Maintenance Treatment of Major Depressive Disorder-Update 2015

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Abstract

These guidelines for the treatment of unipolar depressive disorders systematically review available evidence pertaining to the biological treatment of patients with major depression and 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 assessing and treating patients with these conditions. The relevant data have been extracted primarily from various treatment guidelines and panels for depressive disorders, as well as from meta-analyses/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 five levels of evidence (CE A-F) and five levels of recommendation grades (RG 1–5). This second part of the WFSBP guidelines on depressive disorders covers the management of the maintenance phase treatment, and is primarily concerned with the biological treatment (including pharmacological and hormonal medications, electroconvulsive therapy and other brain stimulation treatments) of adults and also, albeit to a lesser extent, children, adolescents and older adults.

Key words: *major depressive disorder; maintenance treatment; guidelines; pharmacotherapy; antidepressants*

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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. The consideration of the patient's course of illness and treatment history is essential for the implementation of maintenance-phase treatment. Continuation of successful treatment for 6–9 months after remission of the acute depressive episode should be recommended. Even though no definite recommendation can be given as to when prophylactic therapy beyond these 6–9 months is warranted, it is clearly indicated in situations associated with a high risk of recurrence or consequences. 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 5 years), longer-term maintenance therapy is indicated. Besides a high number of previous episodes adverse prognostic indicators for recurrence include, residual symptoms at remission, previous longer episodes and chronicity, more severe previous episodes, onset early in life, concurrent dysthymic disorder ("double depression"), relapse/recurrence after medication withdrawal, previous episode in the last year, concurrent substance abuse or anxiety disorders, and family history of MDD in first degree relatives.

Key elements of long-term treatment of MDD include (1) psychoeducation, (2) pharmacotherapy, and (3) adherence monitoring and improvement, if indicated. Adjunctive depression-targeted psychotherapy such as cognitive behavioural therapy (CBT), and lifestyle strategies should be considered on an individual basis. Because maintenance treatment requires adherence with medication, education and a close therapeutic alliance with patients and their families are essential. Strategies to prepare patients and their families for maintenance treatment should include 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. It is also essential to regularly check adherence to medication and to detect breakthrough symptoms early.

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 (in case of successful lithium augmentation in acute treatment phase). In patients who fail to remain well on either drug alone the combination of antidepressant and lithium is indicated.

Many patients receive antidepressants during the acute and continuation phase, and the best treatment recommendation to prevent recurrence of depression is to continue this medication at the same dose during the maintenance phase. Randomized placebo-controlled studies (usually conducted 1 or 2 years during maintenance treatment) indicate that tricyclic antidepressants (TCAs), irreversible monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRIs) and selective serotonin norepinephrine reuptake inhibitors (SNRIs) are effective in preventing recurrence of depression. Evidence suggests that the "newer" antidepressants may have superior long-term efficacy due to better tolerability compared to traditional antidepressants (e.g., TCAs). In addition they possess a more beneficial safety profile. With respect to lithium therapy, serum lithium levels of 0.6– 0.8 mmol/l (mEq/l) determined 12 h after 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 0.4–1.0 mmol/l depending on individual effectiveness and side effects. There is also preliminary evidence that quetiapine is effective in the maintenance treatment of major depression, whereas the evidence that carbamazepine is an alternative medication in the maintenance treatment of MDD is rather weak. 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 or who do not respond to maintenance medication treatment.

The duration of continuation treatment following remission of the acute depressive episode should be 6–9 months. Treatment length required for maintenance treatment beyond that point is not yet fully determined. Duration may vary from 3 years to lifetime, but in general the more adverse the prognosis, the longer the maintenance therapy. 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 5 years or when remission has been difficult to achieve. Maintenance treatment for 5–10 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.

Withdrawal of antidepressants and lithium, in particular after longer-term use (e.g., longer than

6 months), should always be gradual, with dose reductions over at least 3 months. Abrupt cessation of antidepressants after longer-term use can lead to withdrawal syndromes. In case of lithium rapid withdrawal can lead to rebound relapse and recurrence. When symptoms return during or after withdrawal of lithium or antidepressants, full-dose maintenance treatment should be resumed.

1. Long-term treatment of major depressive disorder

1.1. Introduction

Major depressive disorder, in its classic form, presents as a recurrent disorder (Angst 1986; Kiloh et al. 1988; Judd 1997; Anderson et al. 2008). Fifty to 85% of the patients who have a major depressive episode will have another episode (Mueller et al. 1999; American Psychiatric Association 2000; Andrews 2001). 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 (Consensus Development Panel 1985). Among other risk factors for recurrence of MDD are: prior history of multiple episodes, early age at onset, persistence of dysthymic symptoms after recovery from an episode, 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).

The long-term course of 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 (including cognitive impairment) and social or occupational impairment persist. 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 2 years of illness (Keller et al. 1986; Scott 1988; American Psychiatric Association 2000; Judd and Akiskal 2000). Epidemiological and prospective clinical follow-up studies have also documented that the typical course of 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 (Judd and Akiskal 2000).

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). Patients with an early onset (between age 15 and 25) and a high number of recurrences early in life are at risk to develop (hypo-)manic episodes (and convert to bipolar disorder) (Angst et al. 2013; Miret et al. 2013). Individuals suffering from either dysthymia alone or "double depression" have significantly greater impairment in functioning than those with present either 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 high risk for early episode relapse and a significantly more chronic future course of illness. Full recovery from MDD is associated with significant delays in treatment emergent episode 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 and evidence-based recommendations for the maintenance treatment of patients with MDD. They were developed by the authors and arrived at by consensus with the WFSBP Task Force on Unipolar Depressive Disorders consisting of 56 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. In case it was not possible to reach a consensus within the Task Force on a particular issue, the chairman and co-chairmen had to make a final decision.

These guidelines are intended for use in clinical practice by *all* physicians assessing 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, lithium, other psychopharmacological and hormonal medications, repetitive transcranial magnetic stimulation and ECT) of unipolar depressive disorders in young and middle-aged adults, but also, albeit to a lesser extent, of children, adolescents and older adults. They do not address depression occurring in bipolar affective disorders (which are covered by separate WFSBP guidelines) (Grunze et al. 2010, 2013). The management of the acute and continuation treatment of MDD was covered in Part 1 of the WFSBP guidelines (Bauer et al. 2013a). This second part of the guidelines covers management of the maintenance-phase treatment of MDD. 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 original development of these guidelines (Bauer et al. 2002b) have been extracted from the following sources: Agency for Health Care Policy and Research (AHCPR) Depression Guidelines Panel (1993); AHCPR Evidence Report on Treatment of Depression: Newer Pharmacotherapies (1999); American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Revision (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 (2000); American Academy of Child and Adolescent Psychiatry, Practice Parameters for the Assessment and Treatment of Children and Adolsecents with Depressive Disorders (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.

For the 2014 update, apart from a systematic update search in the MEDLINE database, the following guidelines published in English were consulted: the Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders as well as the clinical guidelines for the management of MDDs in adults (Kennedy et al. 2009a, 2009b; Lam et al. 2009; Parikh et al. 2009; Patten et al. 2009; Ravindran et al. 2009; Beaulieu et al. 2012; Bond et al. 2012; McIntyre et al. 2012a, 2012b; Ramasubbu et al. 2012a, 2012b; Rosenbluth et al. 2012; Schaffer et al. 2012), the British Association for Psychopharmacology guidelines for treating depressive disorders with antidepressants (Anderson et al. 2008), the Australian and New Zealand clinical practice guidelines for the treatment of depression (Ellis 2004), the NICE guidelines (NICE guidelines 2009), and the German S3 guidelines for the treatment of unipolar depression (Härter et al. 2010). The individual trials upon which the above documents are based were also considered, even if they are not all cited individually.

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

As described by Bandelow et al. (2008), Grunze et al. (2009) and Bauer et al. (2013a), six categories of evidence (CEA to F) were used (Table I):

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

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

RG1: CE A evidence and good risk–benefit ratio
RG2: CE A evidence and moderate risk–benefit ratio
RG3: CE B evidence
RG4: CE C evidence
RG5: CE D evidence.

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 a new episode that appears during recovery (i.e., sustained remission for XYZ days/weeks or longer following the most recent acute episode) (Frank et al. 1991; Kupfer 1993). For this paper maintenance treatment is defined as treatment from 6–9 months and onward after sustained remission, which accordingly is what this guidelines covers. 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 (Dawson et al. 1998; Angst 1999; Paykel 2001) (Table II). 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 (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 and

Table I. Categories of evidence (CE) and recommendation grades (RG).

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

Table II. 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 5 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

improvement, if indicated. Adjunctive depression-targeted psychotherapy (such as CBT) may be included on an individual basis. Because maintenance treatment requires adherence with medication, education and a close therapeutic alliance with patients and their families are essential (Kupfer 1993). Education not only reduces treatment attrition, but also leads to a better outcome (Rush 1999). Strategies to prepare patients and their families for maintenance treatment should include 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 best treatment for the individual is identified.

Other principles of maintenance treatment are to distinguish between spontaneous short-lived 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 (Rush 1999). However, from a practical intention-to-treat perspective the differentiation between blips and true recurrences may be problematic since up front, the clinician cannot know which symptoms will be self-limited (within a short period of time) and which not. Therefore if the symptoms are not severe the clinician may wait for some time (e.g., up to 2 weeks) until changing the treatment unless there is clear evidence from the prior course that mild symptoms are always followed by severe symptoms in an individual patient.

It is also important to regularly check adherence to medication (and, if indicated, help improve adherence), monitor pharmacotherapy for safety and to detect breakthrough symptoms early (Rush 1999; Dodd et al. 2011).

Relapse prevention programs (e.g., a low intensity intervention including enhanced patient education, visits with a depression specialist, telephone calls, symptom monitoring) for depressed patients in primary care may improve antidepressant adherence and depressive symptoms compared with usual primary care (Katon et al. 2001).

The frequency of visits may range from monthly visits to every 3–6 months in stable 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 be also educated to inform the treating physician when and if signs of depression reoccur.

2.2. Pharmacotherapy of maintenance treatment

2.2.1. Evidence of efficacy.

2.2.1.1. Antidepressants. Most patients receive antidepressants during the acute and continuation phase of a depressive episode. The best treatment recommendation to prevent recurrence/relapse 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 (CE A, RG 1). Randomized placebo-controlled studies of antidepressants in the prophylactic treatment of depression (usually, with a few exceptions (Lepine et al. 2004), enriched for acute response and tolerability regarding the antidepressant to be tested (Licht 2013, 1- or 2-year duration) indicate that:

TCAs (amitriptyline, imipramine, nortriptyline, maprotiline) (CE A, RG 2), MAO inhibitors (phenelzine, tranylcypromine) (CE A, RG 2) (Agency for Health Care Policy and Research 1993; Solomon and Bauer 1993; Montgomery 1994; Müller-Oerlinghausen 1999; American Psychiatric Association 2000; Paykel 2001; van den Broek et al. 2006), SSRIs (citalopram (Hochstrasser et al. 2001; Klysner et al. 2002)) (CE A, RG 1), escitalopram (Rapaport et al. 2004; Kornstein et al. 2006)) (CE A, RG 1), fluoxetine (Gilaberte et al. 2001; Keller et al. 2007)) (CE A, RG 2), fluvoxamine (Terra and Montgomery 1998) (CE A, RG 2), paroxetine (Montgomery and Dunbar 1993) (CE A, RG 1) and sertraline (Lepine et al. 2004)] (CE A, RG 1) and SNRIs (venlafaxine (Montgomery et al. 2004; Kocsis et al. 2007)) (CE

A, RG 2) and duloxetine (Perahia et al. 2009; Kelin et al. 2010) (CE A, RG 2) and vortioxetine (Boulenger et al. 2012) (CE B, RG 3) are effective in preventing recurrence of depression. As an example of well-designed recent studies underlining the importance of antidepressants in the maintenance treatment of depression, the PREVENT ("Prevention of recurrent episodes of depression with venlafaxine for two years") study should be mentioned. In this multi-phase study patients were initially randomly assigned to double-blind treatment with venlafaxine extended release (ER) (75–300 mg/day) or fluoxetine (20–60 mg/day) for 10 weeks of acute treatment; responders then received 6 months of continuation treatment. Those who remained responders were enrolled into a 12-month maintenance period. Venlafaxine ER responders were randomly assigned to receive double-blind treatment with venlafaxine ER or placebo. Fluoxetine responders were not randomly assigned but continued taking fluoxetine in order to maintain the blind during the maintenance study (Kocsis et al. 2007). Venlafaxine ER was effective in preventing long-term recurrence when compared with placebo, with a significant reduction in likelihood of recurrence and significantly longer time to recurrence after both 1 and 2 years of maintenance therapy. Recurrence rates in the first and second maintenance periods (1 and 2 years) for patients receiving placebo were similar (42 vs. 45%), but recurrence rates for patients receiving venlafaxine ER decreased dramatically (23 vs. 8%).

2.2.1.2. Lithium. The use of lithium as maintenance therapy for recurrent unipolar depression is well established (CE A, RG 2) (Schou 1997; Davis et al. 1999; Bauer et al. 2000, 2014; Coppen 2000; Paykel 2001; Bschor et al. 2002; Davis 2006). Three meta-analyses have examined the efficacy of lithium in the maintenance treatment of unipolar depression. Two meta-analysis found evidence that lithium is more effective than placebo in preventing recurrence of unipolar depressive illness (Souza and Goodwin 1991; Burgess et al. 2001), but only in one the results were statistically significant (Souza and Goodwin 1991). The most recent meta-analysis concluded that there is adequate efficacy for lithium or antidepressants preventing relapse/recurrence in unipolar affective disorder; however, their relative efficacy was unknown (Cipriani et al. 2006). Some data suggest that the combination of antidepressant and lithium may be superior to either drug alone (Kim et al. 1990).

Lithium also seems to have a prophylactic effect on recurrence in maintenance treatment after ECT. In a placebo-controlled RCT investigating different treatment strategies after open-label ECT treatment, the recurrence rate was lower for the combination of lithium and nortriptyline vs. nortriptyline alone (Sackeim et al. 2001).

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 (CE B, RG 3) (Coppen et al. 1990; Müller-Oerlinghausen et al. 1992, 1994; Tondo et al. 1997; Schou 2000). A randomized 2.5-year maintenance treatment study in patients with major affective disorder showed significantly less 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). A systematic review concluded that lithium is effective in the prevention of suicide, deliberate self-harm, and death from all causes in patients with mood disorders (Cipriani et al. 2013). In a meta-analysis in unipolar depression, lithium was found to significantly prevent suicide attempts and suicides (Guzzetta et al. 2007). The overall risk of suicides and suicide attempts was 88.5% lower with lithium compared to without lithium (0.17 vs. 1.48% per year). Similar findings were reported for completed suicides (85% risk reduction). In the only prospective randomized placebo-controlled study (52 weeks) in patients with a high suicide risk, 3.6% of placebo-treated subjects committed suicide, but none of the lithium-treated participants ($N = 167$, $P = 0.049$) (Lauterbach et al. 2008).

Serum lithium levels of 0.6–0.8 mmol/l (mEq/l) drawn 12 h after last lithium intake are usually recommended for maintenance treatment of mood disorders (Schou 1989; Severus et al. 2008; Malhi et al. 2011; Nolen and Weisler 2013). Serum lithium levels should be determined not earlier than 5–7 days from the first dose intake or after change of dosage during maintenance therapy to achieve steady state level. However, the "optimal" serum lithium level may vary somewhat from patient to patient in the range of 0.4–1.0 mmol/l depending on individual effectiveness and tolerability of side effects (Schou 1989). These recommended serum lithium levels are usually achieved with a daily dose of about 900 mg (dosage varies depending on availability of lithium tablets) to 1200 or 1500 mg lithium carbonate (600–1000 mg for Asian patients) in patients 60 years of age or younger, or 400/450 to 800/900 mg lithium carbonate in older patients. There is no difference in efficacy whether lithium tablets are administered once or twice per day. Some patients find that a single daily dose facilitates long-term treatment adherence and

reduces side effects (Mosolov et al. 1997). In general, extended release forms of lithium are better tolerated.

2.2.1.3. Quetiapine. Atypical antipsychotics have been investigated in unipolar depression as an augmentation strategy (Vieta and Colom 2011). Several RCTs have proven their efficacy in acute treatment studies (Nelson and Papakostas 2009). Recently one RCT demonstrated the superiority of quetiapine in maintenance monotherapy treatment to prevent relapse/recurrence for MDD (CE B, RG 3) (Liebowitz et al. 2010). Patients with a MDD had an open-label run-in (4–8 weeks), then an open-label stabilization (12–18 weeks, both with quetiapine XR 50–300 mg/day) followed by a randomization (up to 52 weeks) to quetiapine or placebo. Risk of recurrence of depressive event was significantly reduced by 66% in patients randomized to continue with quetiapine versus patients randomized to switch to placebo. Safety and tolerability data of quetiapine in this study were consistent with the known profile of quetiapine.

2.2.1.4. 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 is carbamazepine (CE C1, RG 4). Carbamazepine has been studied in small double-blind comparator trials with lithium in recurrent major depression (for more information on study results see Section 2.2.2 below) (Placidi et al. 1986; Simhandl et al. 1993). Recommended serum levels of 4–12 μg/ml (17–50 μmol/l), measured 12 h after the last drug intake (and not sooner than 5 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 adherence and excessive adverse effects. Maintenance doses average about 800–1600 mg/day, but may be lower in routine clinical practice. To avoid early side effects related to quick dose escalation it is recommended to start with 100 mg/day and increase the dose by 100 mg once every 3 days to achieve the target dose. Because carbamazepine can induce its own hepatic metabolism (via cytochrome CYP450 isoenzymes), determinations of serum carbamazepine should be done every second week for the first 2 months after initial treatment, every second month for the next 6 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 which 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], oxcarbazepine, 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).

2.2.1.5. Hypericum extract WS 5570. The efficacy and safety of *Hypericum extract WS 5570* in preventing relapse/recurrence during 6 months' continuation treatment and 12-month long-term maintenance treatment after recovery from an episode of recurrent depression was investigated in a large RCT with 426 patients (Kasper et al. 2008). Out-patients with a MDE received single-blind treatment with 3×300 mg/day WS 5570 for 6 weeks. Responders were randomized to 3×300 mg/day WS 5570 or placebo for 26 weeks. Recurrence rates during continuation treatment were significantly lower for WS 5570 (51/282 (18.1%)) compared to placebo (37/144 (25.7%)). In addition patients treated with WS 5570 showed a significantly higher decrease in HAMD total score versus baseline compared to those randomized to placebo (CE B, RG 3). In long-term maintenance treatment a prophylactic effect of WS 5570 was observed in patients with an early onset of depression as well as in those with a high degree of chronicity. Adverse event rates under WS 5570 were comparable to placebo.

2.2.2. Comparative efficacy

Due to the methodologically challenges to validly conduct them (Licht 2013), there is only a relatively small number of studies that have directly compared different medications for maintenance treatment in recurrent unipolar depression (Solomon and Bauer 1993). Two meta-analyses of studies comparing lithium with antidepressants showed no conclusive advantage for lithium in the prophylaxis of unipolar illness (Souza and Goodwin 1991; Cipriani et al. 2006), while the combination treatment of lithium with an antidepressant proved superior to lithium alone or the antidepressant alone (Kim et al. 1990). In one relatively small randomized, placebo-controlled 2-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 2-year study reported greater 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 did not provide advantage over 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. 1996).

A randomized 3-year maintenance study in a group of patients with major affective disorder showed equal efficacy between lithium and carbamazepine (Placidi et al. 1986); for these two medications, similar results were obtained in a randomized 2-year study in unipolar depression (Simhandl et al. 1993). However, lack of superiority does not necessarily imply equivalent efficacy (Vieta and Cruz 2012). 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 (RG C, CE 4).

In the largest and probably most influential study of the use of antidepressants in maintenance treatment, a randomized 3-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 8 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 3-year study, had remitted on the combination of imipramine and IPT, and all had remained well for 4 months of continuation therapy prior to randomization. A subsequent additional 2-year placebo-controlled study of the patients who completed the 3-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. 2013) may have superior long-term efficacy and better tolerability compared with traditional TCAs (Montgomery 1999). A randomized, placebo-controlled 2-year study comparing the efficacy of mirtazapine with that of amitriptyline found that the time to relapse/recurrence was significantly longer in the mirtazapine group (CE B, RG 3) (Montgomery et al. 1998). Similarly, a double-blind 1-year study reported significantly greater improvement in some of the outcome measures in the venlafaxine group compared with imipramine (CE B, RG 3) (Shrivastava et al. 1994).

The latest trial investigating the maintenance treatment of unipolar depression of different antidepressants was the PREVENT study, comparing the efficacy of venlafaxine and fluoxetine for the prevention of recurrence in patients with a history of recurrent MDD for 2 years. The estimated probability of not experiencing a recurrence was 71.9% for venlafaxine and 55.8% for fluoxetine across 24 months of maintenance treatment without showing significant superiority of venlafaxine; however, a significant treatment-by-time interaction showing superiority of venlafaxine was observed (Thase et al. 2011).

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, and they should be as minimal as possible. Even mild to moderate side effects during maintenance treatment may lead to non-adherence with the consequence of symptom worsening and increased risk of recurrence. Using medications with a more favourable side effect profile than the tricyclic antidepressants (TCA) may facilitate patient adherence 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 are the older tricyclics and tetracyclics (for details about side effects of antidepressants see Part 1 of these guidelines, Agency for Health Care Policy and Research 1993; American Psychiatric Association 2000; Bauer et al. 2002a; Peretti et al. 2000), apart from sexual dysfunction (Taylor et al. 2013). However, there is recent concern about the capacity of SSRI antidepressants to reduce bone mineral density, with long-term implications including increased fracture risk (Schwan and Hallberg 2009; Williams et al. 2008).

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 serum lithium level (done one to four times per year, and more frequently if clinically required, e.g., in early stages of treatment, with older patients or after clinical changes have become apparent), thyroid function (e.g., TSH level), parathyroid function (e.g., blood calcium and, if elevated, also parathyroid hormone) and renal function (creatinine, eGFR) (e.g., once or twice a year) is recommended (American Psychiatric Association 1994; Berger et al. 2013; Bschor 2014; Livingstone and Rampes 2006; Schou 1997; Severus and Bauer 2013). The purpose of measuring serum lithium levels is to ensure high serum lithium levels are detected and lowered, and to ensure steps are taken to prevent recurrence in case of abnormally low serum lithium levels. It is also important to educate the patients and their families on the warning signs of lithium toxicity. Among the well-established side effects of lithium treatment are reduced glomerular filtration rate, reduced urinary concentrating ability, hypothyroidism, hyperparathyroidism and weight gain (McKnight et al. 2012). 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 15 or more years of lithium therapy, affection of both glomerular and tubular function seems to be more common (Bendz et al. 2010).

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 1994). Side effects may include: hand tremor (counteracted by a β-blocker), goitre and hypothyroidism (additional administration of L-thyroxine [L-T_4] 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 (e.g., nausea, dyspepsia, loose stools; managed by administering lithium with meals or switching lithium preparations or dose reduction) and in few cases memory impairment/mental slowness (dose reduction) (American Psychiatric Association 1994). The most difficult to treat side effect 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, which inhibits the epithelial sodium channels in collecting tubule cells and therefore should minimize further accumulation of lithium, or a thiazide diuretic may be tried (cave: risk of thiazide-induced hypokalemia).

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 or spontaneously with continued treatment; however, close monitoring is required), mild liver enzyme elevations, and hyponatremia (American Psychiatric Association 1994). Monitoring of laboratory values (blood count, liver enzymes, electrolytes) is recommended two to four times per year during maintenance treatment. Rare, idiosyncratic but potentially fatal side effects of carbamazepine (occurring usually in the first 6 months of treatment) include agranulocytosis, aplastic anemia, hepatic failure, exfoliative dermatitis (e.g., Stevens–Johnson Syndrome) and pancreatitis (American Psychiatric Association 1994). 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 the treatment with carbamazepine.

Preliminary data also show efficacy of quetiapine as a second generation antipsychotic (SGA) in maintenance treatment of unipolar depression (CE B, RG 3). SGA and their negative effect on metabolic function, weight gain as well as tardive dyskinesia should be taken under consideration and are criticized as underestimated in prescribing this group of medication also in unipolar depression (Gao et al. 2011). Drugs with positive acute adjunctive study results, such as aripiprazole, have not been tested in RCTs in maintenance treatment of major depression.

2.2.4. Treatment of symptomatic worsening, recurrence and subsequent maintenance therapy.

Brief, mild depressive short-lived symptoms ("blips") frequently occur during maintenance treatment. As mentioned earlier, 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, among others, evaluation of occult substance abuse, occult physical illness (e.g., thyroid dysfunction) or nonadherence to medication (Rush 1999). Patients experiencing a new depressive episode while taking lithium or an antidepressant may benefit from treatment optimization (e.g., increase of serum lithium level to ≥ 0.6 mmol/l, 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. 2013). Choosing among the drugs available for this indication special emphasis should be put on selecting drugs also efficacious (and approved, if possible) for maintenance treatment. Dependent on the outcome of the acute phase/continuation treatment phase the treatment plan for subsequent maintenance therapy should be designed. This may include CBT for "early warning signs" recognition. Little data from formal studies is available to guide physicians in the maintenance treatment of patients having successfully recovered from a recurrence during standard prophylactic treatment. In principle we recommend to stay on the medication with which remission of the recurrence was achieved, in particular if this medication has also proven efficacious in maintenance treatment of major depression. Besides the established treatment 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, and close monitoring of potential adverse effects associated with such dosages is mandatory (CE C, RG 4).

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. 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 5-year study that patients who benefit the most from continued prophylaxis were those receiving active full-dose medication for at least 5 years (CE B, RG 3) (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 (Lam et al. 2009). 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 5 years or where remission has been difficult to achieve. Maintenance for 5 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 when long-term pharmacotherapy is discontinued, 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 is withdrawn too rapidly), and withdrawal (development of different symptoms related to drug stoppage; typically occurs if TCAs, SSRIs or venlafaxine are abruptly stopped) (Paykel 2001). In clinical practice, antidepressants should always be withdrawn slowly after maintenance therapy. A tapering period of 4–6 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. After discontinuation is complete monitoring should continue during the next couple of months (e.g., particularly for the next 6 months, which appear to be a period of high risk for recurrence to identify those in whom a relapse/recurrence is likely) (Lam et al. 2009). If the full depressive episode recurs during or after discontinuation, a full therapeutic dosage should be promptly re-administered (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 MAO inhibitors, SSRIs and venlafaxine (Lejoyeux and Ades 1997; Edwards and Anderson 1999), but not with agomelatine (Goodwin et al. 2009) or vortioxetine. Data from a RCT showed that discontinuation symptoms are more common with a shorter acting SSRI, such as paroxetine, than with the longer acting agent, such as fluoxetine (Rosenbaum et al. 1998; Tint et al. 2008). 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 MAO inhibitors. 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.

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 10–20% of patients (Akiskal et al. 1995; Angst et al. 1978; Solomon et al. 1997), with a conversion rate between 1.5 and 2.0% of unipolar patients per year (Angst et al. 2005; Baldessarini et al. 2013; Dudek et al. 2013). Antidepressants, particularly tricyclics, may precipitate mania in some patients with a formal diagnosis of unipolar depression (Altshuler et al. 1995). Early age at onset of MDD, high number of episodes early in life, greater acuteness, pleomorphic psychopathology, and high rates of substance abuse have been identified as clinical predictors of the switch to (hypo)mania (Akiskal et al. 1995; Valenti et al. 2012; Pacchiarotti et al. 2013). In addition family history of bipolar disorder might be a helpful predictor for a switch to bipolar disorder among patients with recurrent unipolar depression (Bowden 2005). If a switch to (hypo) mania occurs during the maintenance phase treatment in unipolar depression, the diagnosis should be revisited, and discontinuation of the antidepressant and concomitant treatment of the manic episode is essential (for more information on the treatment of (hypo)mania, see WFSBP Guidelines for the Treatment of Bipolar Disorder) (Grunze et al. 2009).

2.5. Electroconvulsive therapy (ECT).

During the last decade, RCTs have reported on the successful use of ECT in the maintenance phase of treatment (CE D, RG 5) (Sackeim et al. 2001; Kellner et al. 2006). Periodic (maintenance) ECT has been recommended for patients who fully responded during the acute treatment phase and especially for those who are not eligible or who fail maintenance medication treatment. A recent review listed six prospective naturalistic studies (Wijkstra et al. 2000; Datto et al. 2001; Swoboda et al. 2001; Rami-Gonzalez et al. 2003; Vothknecht et al. 2003; Rami et al. 2004; Odeberg et al. 2008) and two RCTs (Kellner et al. 2006; Navarro et al. 2008) examining continuation- (C-ECT) or maintenance-ECT (M-ECT) (Petrides et al. 2011). The CORE-study was the first large RCT to compare the relative efficacy of C-ECT to a combination pharmacotherapy regimen. A total of 531 patients with unipolar MDD were enrolled into the acute ECT phase (Kellner et al. 2006). A total of 201 patients were enrolled into the continuation phase of the study and were randomized to receive 6 months of C-ECT or continuation pharmacotherapy (C-PHARM). C-PHARM consisted of the combination of lithium and nortriptyline and patients were evaluated at the same interval as in the C-ECT arm. The relapse/recurrence rates at 6 months did not differ statistically between the two arms – 37.1% for C-ECT and 31.6% for C-PHARM – and were comparable to those reported in the similarly designed study of (Sackeim et al. 2001) for the combination of lithium and nortriptyline (39%), and better than those reported for nortriptyline alone. Usually, about one or two ECT treatments per month is recommended.

M-ECT are valuable treatment modalities to prevent relapse and recurrence of mood disorders in patients who have responded to an index course of ECT. Current research is seeking to assess the role of combined antidepressant pharmacotherapy plus ECT in continuation phases of maintenance ECT.

A recent randomized study demonstrated cognitive-behavioural group therapy plus medication to be superior over C-ECT plus medication in the continuation phase (6 months) after a successful course of ECT (Brakemeier et al. 2014).

2.6 Other treatment options

2.6.1 Repetitive transcranial magnetic stimulation (rTMS)

TMS is one of the few fundamentally new treatments introduced into psychiatric practice for a considerable number of years (Gaynes et al. 2014; Lepping et al. 2014). The majority of previous clin-

ical studies have indicated that repetitive transcranial magnetic stimulation (rTMS) may have antidepressant effects and its effects have now been confirmed in several large-scale clinical trials and a number of meta-analyses. There have been more than 30 randomized controlled rTMS trials involving patients with MDD. Two large, multicentre, randomized controlled trials have shown superior antidepressant efficacy of rTMS over sham rTMS, although the number of responders to treatment is relatively modest. The vast majority of the trials conducted on the technique have evaluated the efficacy of high-frequency rTMS applied to the left dorsolateral prefrontal cortex (Berlim et al. 2014).

Maintenance rTMS for depression has only been explored very rarely (CE C1, RG4) (O'Reardon et al. 2005). To date there are no sham-controlled studies supporting its efficacy. There are different maintenance strategies for rTMS: Models are described with weekly or 2-weekly single rTMS sessions, often with a progressive decrease in session frequency over time and often combined with mainenance ECT. However there are more intensive treatment regimens for maintenance rTMS (Fitzgerald and Daskalakis 2012). Additional antidepressant medication as maintenance treatment after acute rTMS also seems to be a reasonable advice (Schule et al. 2003).

2.6.2. Deep brain stimulation (DBS). DBS is being evaluated as an option for treatment resistant major depressive episodes (Smith 2014). DBS uses stereotactically implanted intracerebral electrodes connected to a neurostimulator (implanted in the chest wall) to interfere continuously (though reversibly) with the functions of neurons surrounding the electrodes. Preliminary findings show promising results that DBS of certain brain regions may significantly reduce symptoms in treatment-resistant MDD (Schlaepfer et al. 2013). If DBS is used, it is currently used as a continuous treatment. To date, there are no studies regarding long-term results of DBS or specifically maintenance treatment.

2.6.3. Vagus nerve stimulation (VNS). VNS has been widely used in the United States and Europe for persistent treatment refractory seizure conditions. FDA approval for VNS was received in 2005 as an adjunct therapy for treatment resistant MDD, based on a series of clinical trials (Rush et al. 2000). Although response rates with VNS have been modest in the acute phase of treatment (Daban et al. 2008), open label extension phases suggest an increased effect over time (Nahas et al. 2005). A small electrical current is applied to the left vagus nerve using an implanted electrical generator (typically implanted in the chest region). The lead from the device is attached to the cervical region of the vagus. The patient receives around-the-clock stimulation, typically with stimulation periods, lasting 30 s, with 5 min of rest between trains. In a recent large, prospective, double-blind trial that used VNS in treatment resistant depression, medium and high VNS stimulation dose was not more effective than low dose (pseudo-placebo) in the acute treatment, but in post-hoc analyses they were superior to low dose VNS in long-term treatment (Aaronson et al. 2013). Concerning long-term- and maintenance treatment, in this trial continued antidepressant improvement was seen in all three groups in the long-term phase underlining the potentially successive antidepressive effects in the long-run. However, RCTs examining VNS in maintenance treatment of unipolar depression are missing yet (CE C, RG 4).

2.7. Psychotherapy

Similarly to Part 1 of these WFSBP guidelines (Bauer et al. 2013), these guidelines here focus on biological (somatic) treatments. 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. It also seems important to mention that research in psychotherapy has been hampered by the fact that placebo psychotherapy does not exist as, similar to the placebo effect in clinical practice, every interaction between humans, e.g., in psychotherapy, is inevitably embedded in a psychosocial context which has a specific meaning and gives rise to distinct expectations in the individuals involved (patient, psychotherapist) – and can therefore, by definition, not be inactive. Furthermore, blinding psychotherapeutic approaches, in contrast to psychopharmacological treatment approaches, has not been feasible. Consequently establishing the proof of efficacy in a methodologically comparable way to psychopharmacological interventions (double-blind, placebo-controlled trials) has been impossible (Hegerl et al. 2011). Having said this, there is now ample evidence to support the efficacy of CBT in the maintenance treatment of major depression, either alone or in combination with antidepressants (Vittengl et al. 2007), with the effect size varying dependent on many variables, such as the control condition (Lynch et al. 2010; Stangier et al. 2013). Regarding the mode of delivery, face to face CBT is more effective than telephone-administered CBT at follow-up (Mohr et al. 2012). Similarly the majority of data support the efficacy of mindfulness-based cognitive therapy

(MBCT) (Segal et al. 2010; Piet and Hougaard 2011) and interpersonal psychotherapy (IPT) (Cuijpers et al. 2011) in this indication. Furthermore initial data hint at the effectiveness of family psychoeducation (Shimazu et al. 2011). Internet based approaches are increasingly being utilized (Christensen et al. 2004). Lastly, attention to lifestyle factors including smoking cessation, diet and exercise is of value (Berk et al. 2013). Smoking cessation has latterly been shown to reduce depression risk (Taylor et al. 2014).

2.8. Maintenance-phase treatment of MDD in special age groups

2.8.1. Children and adolescents. In recent years several studies have been performed to examine efficacy of antidepressants and their potential to prevent new depressive episodes after remission or response in children and adolescents (Brent et al. 2008; Cheung et al. 2008; Emslie et al. 2008). In those studies SSRIs (fluoxetine, sertraline) and SNRIs (venlafaxine) were used. There is evidence of an effect favouring medication over placebo in preventing the next episode of depression measured by relapse-recurrence rates. There was no statistically significant difference in suicide-related behaviours reported for those receiving medication compared with placebo. A Cochrane review on this topic summarizes that there is limited evidence that continued medication is more effective than placebo in preventing new episodes (Cox et al. 2012).

2.8.2. Older adults. The efficacy and safety of antidepressants in preventing recurrence of MDD in patients in older age have also been examined during the last decade for several compounds in different RCTs. The efficacy and safety of nortriptyline in preventing recurrence of major depressive episodes in patients older than 59 were well determined in a 3-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 (CE A, RG 2) (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 some 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 (CE B, RG 3) (Georgotas et al. 1989).

The SSRIs were also studied as alternatives to nortriptyline in the maintenance treatment of recurrent depression in older adults (Reynolds et al. 2001, 2006; Klysner et al. 2002; Gorwood et al. 2007) and showed superiority in preventing recurrence in comparison to placebo (for paroxetine, escitalopram and citalopram, not for sertraline (Wilson et al. 2003)). For example, in a randomized, double-blind, placebo-controlled trial, Reynolds et al. demonstrated that patients 70 years of age or older with major depression who had a response to initial treatment with paroxetine and psychotherapy were less likely to have recurrent depression if they received 2 years of maintenance therapy with paroxetine. However in the study of Wilson et al., sertraline at therapeutic dosage did not provide significant protection against recurrence.

In a current Cochrane Review (Wilkinson and Izmeth 2012) the authors found evidence that continuing antidepressant medication for 12 months appears to be helpful but limit their recommendation because this is based on only three small studies with few participants using differing classes of antidepressants in clinically heterogeneous populations. However, older patients with depression should also be treated like younger patients under consideration of side effects. Currently there are no data demonstrating differences in efficacy between AD classes. However TCAs should be started with a reduced dosage.

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References

Aaronson ST, Carpenter LL, Conway CR, Reimherr FW, Lisanby SH, Schwartz TL, et al. 2013. Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: acute and chronic effects. Brain Stimul 6(4):631–640.

Agency for Health Care Policy and Research. 1993. Depression in primary care: detection, diagnosis, and treatment. Agency for Health Care Policy and Research. Clin Pract Guidel Quick Ref Guide Clin(5):1–20.

Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Keller M, et al. 1995. Switching from "unipolar" to bipolar II. An 11-year prospective study of clinical and temperamental predictors in 559 patients. Arch Gen Psychiatry 52(2):114–123.

Altshuler LL, Post RM, Leverich GS, Mikalauskas K, Rosoff A, Ackerman L. 1995. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 152(8):1130–1138.

American Psychiatric Association. 1994. Practice guideline for the treatment of patients with bipolar disorder. American Psychiatric Association. Am J Psychiatry 151(12 Suppl):1–36.

American Psychiatric Association. 2000. Practice guideline for the treatment of patients with major depressive disorder (revision). American Psychiatric Association. Am J Psychiatry 157(4 Suppl):1–45.

Anderson IM, Ferrier IN, Baldwin RC, Cowen PJ, Howard L, Lewis G, et al. 2008. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. J Psychopharmacol 22(4):343–396.

Anderson IM, Nutt DJ, Deakin JF. 2000. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. British Association for Psychopharmacology. J Psychopharmacol 14(1):3–20.

Andrews G. 2001. Should depression be managed as a chronic disease? Br Med J 322(7283):419–421.

Angst J. 1986. The course of affective disorders. Psychopathology 19(Suppl 2):47–52.

Angst J. 1999. Major depression in 1998: are we providing optimal therapy? J Clin Psychiatry 60(Suppl 6):5–9.

Angst J, Felder W, Frey R, Stassen HH. 1978. The course of affective disorders. I. Change of diagnosis of monopolar, unipolar, and bipolar illness. Arch Psychiatr Nervenkr 226(1):57–64.

Angst J, Gamma A, Bowden CL, Azorin JM, Perugi G, Vieta E, et al. 2013. Evidence-based definitions of bipolar-I and bipolar-II disorders among 5,635 patients with major depressive episodes in the Bridge Study: validity and comorbidity. Eur Arch Psychiatry Clin Neurosci 263(8):663–673.

Angst J, Sellaro R, Stassen HH, Gamma A. 2005. Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. J Affect Disord 84(2–3):149–157.

Baldessarini RJ, Faedda GL, Offidani E, Vazquez GH, Marangoni C, Serra G, et al. 2013. Antidepressant-associated mood-switching and transition from unipolar major depression to bipolar disorder: a review. J Affect Disord 148(1):129–135.

Bandelow B, Zohar J, Hollander E, Kasper S, Moller HJ, Zohar J, et al. 2008. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders – first revision. World J Biol Psychiatry 9(4): 248–312.

Bauer M, Adli M, Ricken R, Severus E, Pilhatsch M. 2014. Role of lithium augmentation in the management of major depressive disorder. CNS Drugs 28(4):331–342.

Bauer M, Bschor T, Kunz D, Berghofer A, Strohle A, Müller-Oerlinghausen B. 2000. Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. Am J Psychiatry 157(9):1429–1435.

Bauer M, Pfennig A, Severus E, Whybrow PC, Angst J, Moller HJ. 2013. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. World J Biol Psychiatry 14(5):334–385.

Bauer M, Priebe S, Berghofer A, Bschor T, Kiesslinger U, Whybrow PC. 2001. Subjective response to and tolerability of long-term supraphysiological doses of levothyroxine in refractory mood disorders. J Affect Disord 64(1):35–42.

Bauer M, Whybrow PC, Angst J, Versiani M, Moller HJ. 2002a. 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. World J Biol Psychiatry 3(1):5–43.

Bauer M, Whybrow PC, Angst J, Versiani M, Moller HJ. 2002b. 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. World J Biol Psychiatry 3(2):69–86.

Beaulieu S, Saury S, Sareen J, Tremblay J, Schutz CG, McIntyre RS, et al. 2012. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid substance use disorders. Ann Clin Psychiatry 24(1):38–55.

Bendz H, Schon S, Attman PO, Aurell M. 2010. Renal failure occurs in chronic lithium treatment but is uncommon. Kidney Int 77(3):219–224.

Berger M, Riedel M, Tomova N, Obermeier M, Dittmann S, Moeller H-J, et al. 2013. Do current screening recommendations allow for early detection of lithium-induced hyperparathyroidism in patients with bipolar disorder? Int J Bipolar Disord 1:7.

Berk M, Sarris J, Coulson CE, Jacka FN. 2013. Lifestyle management of unipolar depression. Acta Psychiatr Scand Suppl(443): 38–54.

Berlim MT, Van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. 2014. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med 44(2):225–239.

Bocchetta A, Ardau R, Burrai C, Chillotti C, Quesada G, Del ZM. 1998. Suicidal behavior on and off lithium prophylaxis in a group of patients with prior suicide attempts. J Clin Psychopharmacol 18(5):384–389.

Bond DJ, Hadjipavlou G, Lam RW, McIntyre RS, Beaulieu S, Schaffer A, et al. 2012. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid attention-deficit/hyperactivity disorder. Ann Clin Psychiatry 24(1):23–37.

Boulenger JP, Loft H, Florea I. 2012. A randomized clinical study of Lu AA21004 in the prevention of relapse in patients with major depressive disorder. J Psychopharmacol 26(11): 1408–1416.

Bowden CL. 2005. A different depression: clinical distinctions between bipolar and unipolar depression. J Affect Disord 84(2–3):117–125.

Brakemeier EL, Merkl A, Wilbertz G, Quante A, Regen F, Buhrsch N, et al. 2014. Cognitive-behavioral therapy as

continuation treatment to sustain response after electroconvulsive therapy in depression: a randomized controlled trial. Biol Psychiatry 76(3):194–202.

Brent D, Emslie G, Clarke G, Wagner KD, Asarnow JR, Keller M, et al. 2008. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. J Am Med Assoc 299(8):901–913.

Bschor T. 2014. Lithium in the treatment of major depressive disorder. Drugs 74(8):855–862.

Bschor T, Berghofer A, Strohle A, Kunz D, Adli M, Müller-Oerlinghausen B, et al. 2002. How long should the lithium augmentation strategy be maintained? A 1-year follow-up of a placebo-controlled study in unipolar refractory major depression. J Clin Psychopharmacol 22(4):427–430.

Burgess S, Geddes J, Hawton K, Townsend E, Jamison K, Goodwin G. 2001. Lithium for maintenance treatment of mood disorders. Cochrane Database Syst Rev(3):CD003013.

Cheung A, Kusumakar V, Kutcher S, Dubo E, Garland J, Weiss M, et al. 2008. Maintenance study for adolescent depression. J Child Adolesc Psychopharmacol 18(4):389–394.

Christensen H, Griffiths KM, Jorm AF. 2004. Delivering interventions for depression by using the internet: randomised controlled trial. Br Med J 328(7434):265.

Cipriani A, Hawton K, Stockton S, Geddes JR. 2013. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. Br Med J 346:f3646.

Cipriani A, Smith K, Burgess S, Carney S, Goodwin G, Geddes J. 2006. Lithium versus antidepressants in the long-term treatment of unipolar affective disorder. Cochrane Database Syst Rev(4):CD003492.

Consensus Development Panel. 1985. NIMH/NIH Consensus Development Conference statement. Mood disorders: pharmacologic prevention of recurrences. Consensus Development Panel. Am J Psychiatry 142(4):469–476.

Coppen A. 2000. Lithium in unipolar depression and the prevention of suicide. J Clin Psychiatry 61(Suppl 9):52–56.

Coppen A, Standish-Barry H, Bailey J, Houston G, Silcocks P, Hermon C. 1990. Long-term lithium and mortality. Lancet 335(8701):1347.

Cox GR, Fisher CA, De SS, Phelan M, Akinwale OP, Simmons MB, et al. 2012. Interventions for preventing relapse and recurrence of a depressive disorder in children and adolescents. Cochrane Database Syst Rev 11:CD007504.

Cuijpers P, Geraedts AS, van OP, Andersson G, Markowitz JC, van SA. 2011. Interpersonal psychotherapy for depression: a meta-analysis. Am J Psychiatry 168(6):581–592.

Daban C, Martinez-Aran A, Cruz N, Vieta E. 2008. Safety and efficacy of Vagus Nerve Stimulation in treatment-resistant depression. A systematic review. J Affect Disord 110(1–2):1–15.

Datto CJ, Levy S, Miller DS, Katz IR. 2001. Impact of maintenance ECT on concentration and memory. J ECT 17(3):170–174.

Davis JM. 2006. Lithium maintenance of unipolar depression. In: Bauer M, Grof P, Müller-Oerlinghausen B, editors. London: Informa Healthcare. p 99–108.

Davis JM, Janicak PG, Hogan DM. 1999. Mood stabilizers in the prevention of recurrent affective disorders: a meta-analysis. Acta Psychiatr Scand 100(6):406–417.

Dawson R, Lavori PW, Coryell WH, Endicott J, Keller MB. 1998. Maintenance strategies for unipolar depression: an observational study of levels of treatment and recurrence. J Affect Disord 49(1):31–44.

Dodd S, Malhi GS, Tiller J, Schweitzer I, Hickie I, Khoo JP, et al. 2011. A consensus statement for safety monitoring guidelines of treatments for major depressive disorder. Aust NZ J Psychiatry 45(9):712–725.

Dudek D, Siwek M, Zielinska D, Jaeschke R, Rybakowski J. 2013. Diagnostic conversions from major depressive disorder into bipolar disorder in an outpatient setting: results of a retrospective chart review. J Affect Disord 144(1–2):112–115.

Edwards JG, Anderson I. 1999. Systematic review and guide to selection of selective serotonin reuptake inhibitors. Drugs 57(4):507–533.

Ellis P. 2004. Australian and New Zealand clinical practice guidelines for the treatment of depression. Aust NZ J Psychiatry 38(6):389–407.

Emslie GJ, Kennard BD, Mayes TL, Nightingale-Teresi J, Carmody T, Hughes CW, et al. 2008. Fluoxetine versus placebo in preventing relapse of major depression in children and adolescents. Am J Psychiatry 165(4):459–467.

Fitzgerald PB, Daskalakis ZJ. 2012. A practical guide to the use of repetitive transcranial magnetic stimulation in the treatment of depression. Brain Stimul 5(3):287–296.

Frank E, Kupfer DJ, Perel JM, Cornes C, Jarrett DB, Mallinger AG, et al. 1990. Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry 47(12):1093–1099.

Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, et al. 1991. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 48(9): 851–855.

Gao K, Kemp DE, Fein E, Wang Z, Fang Y, Ganocy SJ, et al. 2011. Number needed to treat to harm for discontinuation due to adverse events in the treatment of bipolar depression, major depressive disorder, and generalized anxiety disorder with atypical antipsychotics. J Clin Psychiatry 72(8):1063–1071.

Gaynes BN, Lloyd SW, Lux L, Gartlehner G, Hansen RA, Brode S, et al. 2014. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. J Clin Psychiatry 75(5):477–489.

Georgotas A, McCue RE, Cooper TB. 1989. A placebo-controlled comparison of nortriptyline and phenelzine in maintenance therapy of elderly depressed patients. Arch Gen Psychiatry 46(9):783–786.

Gilaberte I, Montejo AL, de la Gandara J, Perez-Sola V, Bernardo M, Massana J, et al. 2001. Fluoxetine in the prevention of depressive recurrences: a double-blind study. J Clin Psychopharmacol 21(4):417–424.

Goodwin GM, Emsley R, Rembry S, Rouillon F. 2009. Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: a 24-week randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 70(8):1128–1137.

Gorwood P, Weiller E, Lemming O, Katona C. 2007. Escitalopram prevents relapse in older patients with major depressive disorder. Am J Geriatr Psychiatry 15(7):581–593.

Greenhouse JB, Stangl D, Kupfer DJ, Prien RF. 1991. Methodologic issues in maintenance therapy clinical trials. Arch Gen Psychiatry 48(4):313–318.

Greil W, Ludwig-Mayerhofer W, Erazo N, Engel RR, Czernik A, Giedke H, et al. 1996. Comparative efficacy of lithium and amitriptyline in the maintenance treatment of recurrent unipolar depression: a randomised study. J Affect Disord 40(3):179–190.

Grof P. 1998. Has the effectiveness of lithium changed? Impact of the variety of lithium's effects. Neuropsychopharmacology 19(3):183–188.

Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, et al. 2009. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. World J Biol Psychiatry 10(2):85–116.

Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, et al. 2010. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression. World J Biol Psychiatry 11(2):81–109.

Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, et al. 2013. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. World J Biol Psychiatry 14(3):154–219.

Guzzetta F, Tondo L, Centorrino F, Baldessarini RJ. 2007. Lithium treatment reduces suicide risk in recurrent major depressive disorder. J Clin Psychiatry 68(3):380–383.

Haddad PM. 2001. Antidepressant discontinuation syndromes. Drug Saf 24(3):183–197.

Härter M, Klesse C, Bermejo I, Bschor T, Gensichen J, Harfst T, et al. 2010. [Evidence-based therapy of depression: S3 guidelines on unipolar depression]. Nervenarzt 81(9):1049–1068.

Hegerl U, Allgaier AK, Henkel V, Mergl R. 2011. Can effects of antidepressants in patients with mild depression be considered as clinically significant? J Affect Disord 138(3);183–191.

Hochstrasser B, Isaksen PM, Koponen H, Lauritzen L, Mahnert FA, Rouillon F, et al. 2001. Prophylactic effect of citalopram in unipolar, recurrent depression: placebo-controlled study of maintenance therapy. Br J Psychiatry 178:304–310.

Judd LL. 1997. The clinical course of unipolar major depressive disorders. Arch Gen Psychiatry 54(11):989–991.

Judd LL, Akiskal HS. 2000. Delineating the longitudinal structure of depressive illness: beyond clinical subtypes and duration thresholds. Pharmacopsychiatry 33(1):3–7.

Judd LL, Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, et al. 1998. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. Arch Gen Psychiatry 55(8):694–700.

Judd LL, Paulus MJ, Schettler PJ, Akiskal HS, Endicott J, Leon AC, et al. 2000. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? Am J Psychiatry 157(9):1501–1504.

Kane JM, Quitkin FM, Rifkin A, Ramos-Lorenzi JR, Nayak DD, Howard A. 1982. Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness: a prospective, placebo-controlled comparison. Arch Gen Psychiatry 39(9):1065–1069.

Kasper S, Volz HP, Moller HJ, Dienel A, Kieser M. 2008. Continuation and long-term maintenance treatment with Hypericum extract WS 5570 after recovery from an acute episode of moderate depression – a double-blind, randomized, placebo controlled long-term trial. Eur Neuropsychopharmacol 18(11):803–813.

Katon W, Rutter C, Ludman EJ, Von KM, Lin E, Simon G, et al. 2001. A randomized trial of relapse prevention of depression in primary care. Arch Gen Psychiatry 58(3):241–247.

Kelin K, Berk M, Spann M, Sagman D, Raskin J, Walker D, Perahia D. 2010. Duloxetine 60 mg/day for the prevention of depressive recurrences: post hoc analyses from a recurrence prevention study. Int J Clin Pract 64(6):719–726.

Keller MB, Lavori PW, Rice J, Coryell W, Hirschfeld RM. 1986. The persistent risk of chronicity in recurrent episodes of nonbipolar major depressive disorder: a prospective follow-up. Am J Psychiatry 143(1):24–28.

Keller MB, Trivedi MH, Thase ME, Shelton RC, Kornstein SG, Nemeroff CB, et al. 2007. The prevention of recurrent episodes of depression with venlafaxine for two years (PREVENT) study: outcomes from the acute and continuation phases. Biol Psychiatry 62(12):1371–1379.

Kellner CH, Knapp RG, Petrides G, Rummans TA, Husain MM, Rasmussen K, et al. 2006. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). Arch Gen Psychiatry 63(12):1337–1344.

Kennedy SH, Lam RW, Parikh SV, Patten SB, Ravindran AV. 2009a. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. Introduction. J Affect Disord 117(Suppl 1):S1–2.

Kennedy SH, Milev R, Giacobbe P, Ramasubbu R, Lam RW, Parikh SV, et al. 2009b. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. J Affect Disord 117(Suppl 1): S44–53.

Kiloh LG, Andrews G, Neilson M. 1988. The long-term outcome of depressive illness. Br J Psychiatry 153:752–757.

Kim HR, Delva NJ, Lawson JS. 1990. Prophylactic medication for unipolar depressive illness: the place of lithium carbonate in combination with antidepressant medication. Can J Psychiatry 35(2):107–114.

Klerman GL, Weissman MM. 1989. Increasing rates of depression. J Am Med Asoc 261(15):2229–2235.

Klysner R, Bent-Hansen J, Hansen HL, Lunde M, Pleidrup E, Poulsen DL, et al. 2002. Efficacy of citalopram in the prevention of recurrent depression in elderly patients: placebo-controlled study of maintenance therapy. Br J Psychiatry 181:29–35.

Kocsis JH, Thase ME, Trivedi MH, Shelton RC, Kornstein SG, Nemeroff CB, et al. 2007. Prevention of recurrent episodes of depression with venlafaxine ER in a 1-year maintenance phase from the PREVENT Study. J Clin Psychiatry 68(7): 1014–1023.

Kornstein SG, Bose A, Li D, Saikali KG, Gandhi C. 2006. Escitalopram maintenance treatment for prevention of recurrent depression: a randomized, placebo-controlled trial. J Clin Psychiatry 67(11):1767–1775.

Kovacs M, Devlin B, Pollock M, Richards C, Mukerji P. 1997. A controlled family history study of childhood-onset depressive disorder. Arch Gen Psychiatry 54(7):613–623.

Kupfer DJ. 1993. Management of recurrent depression. J Clin Psychiatry 54(Suppl):29–33.

Kupfer DJ, Frank E, Perel JM. 1989. The advantage of early treatment intervention in recurrent depression. Arch Gen Psychiatry 46(9):771–775.

Kupfer DJ, Frank E, Perel JM, Cornes C, Mallinger AG, Thase ME, et al. 1992. Five-year outcome for maintenance therapies in recurrent depression. Arch Gen Psychiatry 49(10):769–773.

Lam RW, Kennedy SH, Grigoriadis S, McIntyre RS, Milev R, Ramasubbu R, et al. 2009. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. J Affect Disord 117(Suppl 1):S26–S43.

Lauterbach E, Felber W, Müller-Oerlinghausen B, Ahrens B, Bronisch T, Meyer T, et al. 2008. Adjunctive lithium treatment in the prevention of suicidal behaviour in depressive disorders: a randomised, placebo-controlled, 1-year trial. Acta Psychiatr Scand 118(6):469–479.

Lejoyeux M, Ades J. 1997. Antidepressant discontinuation: a review of the literature. J Clin Psychiatry 58(Suppl 7):11–15.

Lepine JP, Caillard V, Bisserbe JC, Troy S, Hotton JM, Boyer P. 2004. A randomized, placebo-controlled trial of sertraline for prophylactic treatment of highly recurrent major depressive disorder. Am J Psychiatry 161(5):836–842.

Lepping P, Schonfeldt-Lecuona C, Sambhi RS, Lanka SV, Lane S, Whittington R, et al. 2014. A systematic review of the clini-

cal relevance of repetitive transcranial magnetic stimulation. Acta Psychiatr Scand 130(5):326–341.
Licht RW. 2013. Is it possible to evaluate true prophylactic efficacy of antidepressants in severely ill patients with recurrent depression? Lessons from a placebo-controlled trial. The fifth trial of the Danish University Antidepressant Group (DUAG-5). J Affect Disord 148(2–3):286–290.
Liebowitz M, Lam RW, Lepola U, Datto C, Sweitzer D, Eriksson H. 2010. Efficacy and tolerability of extended release quetiapine fumarate monotherapy as maintenance treatment of major depressive disorder: a randomized, placebo-controlled trial. Depress Anxiety 27(10):964–976.
Livingstone C, Rampes H. 2006. Lithium: a review of its metabolic adverse effects. J Psychopharmacol 20(3):347–355.
Lynch D, Laws KR, McKenna PJ. 2010. Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials. Psychol Med 40(1):9–24.
Malhi GS, Tanious M, Gershon S. 2011. The lithiumeter: a measured approach. Bipolar Disord 13(3):219–226.
Marraccini RL, Reynolds CF III, Houck PR, Miller MD, Frank E, Perel JM, et al. 1999. A double-blind, placebo-controlled assessment of nortriptyline's side-effects during 3-year maintenance treatment in elderly patients with recurrent major depression. Int J Geriatr Psychiatry 14(12):1014–1018.
McIntyre RS, Alsuwaidan M, Goldstein BI, Taylor VH, Schaffer A, Beaulieu S, et al. 2012a. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid metabolic disorders. Ann Clin Psychiatry 24(1):69–81.
McIntyre RS, Schaffer A, Beaulieu S. 2012b. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid conditions. Ann Clin Psychiatry 24(1):2–3.
McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. 2012. Lithium toxicity profile: a systematic review and meta-analysis. Lancet 379(9817):721–728.
Miret M, Ayuso-Mateos JL, Sanchez-Moreno J, Vieta E. 2013. Depressive disorders and suicide: epidemiology, risk factors, and burden. Neurosci Biobehav Rev 37(10 Pt 1):2372–2374.
Mohr DC, Ho J, Duffecy J, Reifler D, Sokol L, Burns MN, et al. 2012. Effect of telephone-administered vs face-to-face cognitive behavioral therapy on adherence to therapy and depression outcomes among primary care patients: a randomized trial. J Am Med Assoc 307(21):2278–2285.
Montgomery SA. 1994. Long-term treatment of depression. Br J Psychiatry Suppl(26):31–36.
Montgomery SA. 1999. New developments in the treatment of depression. J Clin Psychiatry 60(Suppl 14):10–15.
Montgomery SA, Dunbar G. 1993. Paroxetine is better than placebo in relapse prevention and the prophylaxis of recurrent depression. Int Clin Psychopharmacol 8(3):189–195.
Montgomery SA, Entsuah R, Hackett D, Kunz NR, Rudolph RL. 2004. Venlafaxine versus placebo in the preventive treatment of recurrent major depression. J Clin Psychiatry 65(3):328–336.
Montgomery SA, Reimitz PE, Zivkov M. 1998. Mirtazapine versus amitriptyline in the long-term treatment of depression: a double-blind placebo-controlled study. Int Clin Psychopharmacol 13(2):63–73.
Mosolov SN, Kuzavkova MV, Uzbekov MG, Misionzhhnik EI, Ryzhov AM. 1997. [A comparative clinico-pharmacokinetic study of the use of equivalent daily doses of lithium carbonate and Contemnol]. Zh Nevrol Psikhiatr Im S S Korsakova 97(5):30–33.
Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, et al. 1999. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am J Psychiatry 156(7):1000–1006.
Müller-Oerlinghausen B. 1999. Evidence report: treatment of depression – newer pharmacotherapies. Agency for Health Care Policy and Research (AHCPR). Pharmacopsychiatry 32(6):230–231.
Müller-Oerlinghausen B, Ahrens B, Grof E, Grof P, Lenz G, Schou M, et al. 1992. The effect of long-term lithium treatment on the mortality of patients with manic-depressive and schizoaffective illness. Acta Psychiatr Scand 86(3):218–222.
Müller-Oerlinghausen B, Wolf T, Ahrens B, Schou M, Grof E, Grof P, et al. 1994. Mortality during initial and during later lithium treatment. A collaborative study by the International Group for the Study of Lithium-treated Patients. Acta Psychiatr Scand 90(4):295–297.
Nahas Z, Marangell LB, Husain MM, Rush AJ, Sackeim HA, Lisanby SH, et al. 2005. Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. J Clin Psychiatry 66(9):1097–1104.
Navarro V, Gasto C, Torres X, Masana G, Penades R, Guarch J, et al. 2008. Continuation/maintenance treatment with nortriptyline versus combined nortriptyline and ECT in late-life psychotic depression: a two-year randomized study. Am J Geriatr Psychiatry 16(6):498–505.
Nelson JC, Papakostas GI. 2009. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. Am J Psychiatry 166(9):980–991.
NICE guidelines [CG90] 2009. Depression in adults: the treatment and management of depression in adults [Anonymous].
Nolen WA, Weisler RH. 2013. The association of the effect of lithium in the maintenance treatment of bipolar disorder with lithium plasma levels: a post hoc analysis of a double-blind study comparing switching to lithium or placebo in patients who responded to quetiapine (Trial 144). Bipolar Disord 15(1):100–109.
O'Reardon JP, Blumner KH, Peshek AD, Pradilla RR, Pimiento PC. 2005. Long-term maintenance therapy for major depressive disorder with rTMS. J Clin Psychiatry 66(12):1524–1528.
Odeberg H, Rodriguez-Silva B, Salander P, Martensson B. 2008. Individualized continuation electroconvulsive therapy and medication as a bridge to relapse prevention after an index course of electroconvulsive therapy in severe mood disorders: a naturalistic 3-year cohort study. J ECT 24(3):183–190.
Pacchiarotti I, Baldessarini RJ, Nolen W, Grunze H, Licht R, Post R, et al. 2013. The International Society for Bipolar Disorders (ISBD) Task-Force report on antidepressants use in bipolar disorders. Am J Psychiatry.
Parikh SV, Segal ZV, Grigoriadis S, Ravindran AV, Kennedy SH, Lam RW, et al. 2009. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. II. Psychotherapy alone or in combination with antidepressant medication. J Affect Disord 117(Suppl 1):S15–25.
Patten SB, Kennedy SH, Lam RW, O'Donovan C, Filteau MJ, Parikh SV, et al. 2009. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. I. Classification, burden and principles of management. J Affect Disord 117(Suppl 1):S5–14.
Paykel ES. 2001. Continuation and maintenance therapy in depression. Br Med Bull 57:145–159.
Perahia DG, Maina G, Thase ME, Spann ME, Wang F, Walker DJ, et al. 2009. Duloxetine in the prevention of depressive

recurrences: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 70(5):706–716.
Peretti S, Judge R, Hindmarch I. 2000. Safety and tolerability considerations: tricyclic antidepressants vs. selective serotonin reuptake inhibitors. Acta Psychiatr Scand Suppl 403:17–25.
Petrides G, Tobias KG, Kellner CH, Rudorfer MV. 2011. Continuation and maintenance electroconvulsive therapy for mood disorders: review of the literature. Neuropsychobiology 64(3):129–140.
Piet J, Hougaard E. 2011. The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: a systematic review and meta-analysis. Clin Psychol Rev 31(6):1032–1040.
Placidi GF, Lenzi A, Lazzerini F, Cassano GB, Akiskal HS. 1986. The comparative efficacy and safety of carbamazepine versus lithium: a randomized, double-blind 3-year trial in 83 patients. J Clin Psychiatry 47(10):490–494.
Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, et al. 1984. Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. Arch Gen Psychiatry 41(11):1096–1104.
Ramasubbu R, Beaulieu S, Taylor VH, Schaffer A, McIntyre RS. 2012a. The CANMAT task force recommendations for the management of patients with mood disorders and comorbid medical conditions: diagnostic, assessment, and treatment principles. Ann Clin Psychiatry 24(1):82–90.
Ramasubbu R, Taylor VH, Samaan Z, Sockalingham S, Li M, Patten S, et al. 2012b. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and select comorbid medical conditions. Ann Clin Psychiatry 24(1):91–109.
Rami L, Bernardo M, Boget T, Ferrer J, Portella MJ, Gil-Verona JA, et al. 2004. Cognitive status of psychiatric patients under maintenance electroconvulsive therapy: a one-year longitudinal study. J Neuropsychiatry Clin Neurosci 16(4):465–471.
Rami-Gonzalez L, Salamero M, Boget T, Catalan R, Ferrer J, Bernardo M. 2003. Pattern of cognitive dysfunction in depressive patients during maintenance electroconvulsive therapy. Psychol Med 33(2):345–350.
Rapaport MH, Bose A, Zheng H. 2004. Escitalopram continuation treatment prevents relapse of depressive episodes. J Clin Psychiatry 65(1):44–49.
Ravindran AV, Lam RW, Filteau MJ, Lesperance F, Kennedy SH, Parikh SV, et al. 2009. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. V. Complementary and alternative medicine treatments. J Affect Disord 117(Suppl 1):S54–64.
Reynolds CF III, Alexopoulos GS, Katz IR, Lebowitz BD. 2001. Chronic depression in the elderly: approaches for prevention. Drugs Aging 18(7):507–514.
Reynolds CF III, Dew MA, Pollock BG, Mulsant BH, Frank E, Miller MD, et al. 2006. Maintenance treatment of major depression in old age. New Engl J Med 354(11):1130–1138.
Reynolds CF III, Frank E, Perel JM, Imber SD, Cornes C, Miller MD, et al. 1999a. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. J Am Med Assoc 281(1):39–45.
Reynolds CF III, Perel JM, Frank E, Cornes C, Miller MD, Houck PR, et al. 1999b. Three-year outcomes of maintenance nortriptyline treatment in late-life depression: a study of two fixed plasma levels. Am J Psychiatry 156(8):1177–1181.
Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. 1998. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry 44(2):77–87.
Rosenbluth M, MacQueen G, McIntyre RS, Beaulieu S, Schaffer A. 2012. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid personality disorders. Ann Clin Psychiatry 24(1):56–68.
Rush AJ. 1999. Strategies and tactics in the management of maintenance treatment for depressed patients. J Clin Psychiatry 60(Suppl 14):21–26.
Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C, et al. 2000. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. Biol Psychiatry 47(4):276–286.
Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, et al. 2001. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. J Am Med Assoc 285(10):1299–1307.
Schaffer A, McIntosh D, Goldstein BI, Rector NA, McIntyre RS, Beaulieu S, et al. 2012. The CANMAT task force recommendations for the management of patients with mood disorders and comorbid anxiety disorders. Ann Clin Psychiatry 24(1):6–22.
Schlaepfer TE, Bewernick BH, Kayser S, Madler B, Coenen VA. 2013. Rapid effects of deep brain stimulation for treatment-resistant major depression. Biol Psychiatry 73(12):1204–1212.
Schou M. 1989. Lithium prophylaxis: myths and realities. Am J Psychiatry 146(5):573–576.
Schou M. 1997. Forty years of lithium treatment. Arch Gen Psychiatry 54(1):9–13.
Schou M. 2000. Suicidal behavior and prophylactic lithium treatment of major mood disorders: a review of reviews. Suicide Life Threat Behav 30(3):289–293.
Schule C, Zwanzger P, Baghai T, Mikhaiel P, Thoma H, Moller HJ, et al. 2003. Effects of antidepressant pharmacotherapy after repetitive transcranial magnetic stimulation in major depression: an open follow-up study. J Psychiatr Res 37(2):145–153.
Schwan S, Hallberg P. 2009. SSRIs, bone mineral density, and risk of fractures – a review. Eur Neuropsychopharmacol 19(10):683–692.
Scott J. 1988. Chronic depression. Br J Psychiatry 153:287–297.
Segal ZV, Bieling P, Young T, MacQueen G, Cooke R, Martin L, et al. 2010. Antidepressant monotherapy vs sequential pharmacotherapy and mindfulness-based cognitive therapy, or placebo, for relapse prophylaxis in recurrent depression. Arch Gen Psychiatry 67(12):1256–1264.
Severus E, Bauer M. 2013. Managing the risk of lithium-induced nephropathy in the long-term treatment of patients with recurrent affective disorders. BMC Med 11:34.
Severus WE, Kleindienst N, Seemuller F, Frangou S, Moller HJ, Greil W. 2008. What is the optimal serum lithium level in the long-term treatment of bipolar disorder – a review? Bipolar Disord 10(2):231–237.
Shimazu K, Shimodera S, Mino Y, Nishida A, Kamimura N, Sawada K, et al. 2011. Family psychoeducation for major depression: randomised controlled trial. Br J Psychiatry 198(5):385–390.
Shrivastava RK, Cohn C, Crowder J, Davidson J, Dunner D, Feighner J, et al. 1994. Long-term safety and clinical acceptability of venlafaxine and imipramine in outpatients with major depression. J Clin Psychopharmacol 14(5):322–329.
Simhandl C, Denk E, Thau K. 1993. The comparative efficacy of carbamazepine low and high serum level and lithium carbon-

ate in the prophylaxis of affective disorders. J Affect Disord 28(4):221–231.
Smith DF. 2014. Exploratory meta-analysis on deep brain stimulation in treatment-resistant depression. Acta Neuropsychiatr 26(6):382–384.
Solomon DA, Bauer MS. 1993. Continuation and maintenance pharmacotherapy for unipolar and bipolar mood disorders. Psychiatr Clin North Am 16(3):515–540.
Solomon DA, Keller MB, Leon AC, Mueller TI, Shea MT, Warshaw M, et al. 1997. Recovery from major depression. A 10-year prospective follow-up across multiple episodes. Arch Gen Psychiatry 54(11):1001–1006.
Souza FG, Goodwin GM. 1991. Lithium treatment and prophylaxis in unipolar depression: a meta-analysis. Br J Psychiatry 158:666–675.
Spina E, Pisani F, Perucca E. 1996. Clinically significant pharmacokinetic drug interactions with carbamazepine. An update. Clin Pharmacokinet 31(3):198–214.
Stangier U, Hilling C, Heidenreich T, Risch AK, Barocka A, Schlosser R, et al. 2103. Maintenance cognitive-behavioral therapy and manualized psychoeducation in the treatment of recurrent depression: a multicenter prospective randomized controlled trial. Am J Psychiatry 170(6):624–632.
Swoboda E, Conca A, Konig P, Waanders R, Hansen M. 2001. Maintenance electroconvulsive therapy in affective and schizoaffective disorder. Neuropsychobiology 43(1): 23–28.
Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. 2014. Change in mental health after smoking cessation: systematic review and meta-analysis. Br Med J 348:g1151.
Taylor MJ, Rudkin L, Bullemor-Day P, Lubin J, Chukwujekwu C, Hawton K. 2013. Strategies for managing sexual dysfunction induced by antidepressant medication. Cochrane Database Syst Rev 5:CD003382.
Terra JL, Montgomery SA. 1998. Fluvoxamine prevents recurrence of depression: results of a long-term, double-blind, placebo-controlled study. Int Clin Psychopharmacol 13(2): 55–62.
Thase ME. 1999. Long-term nature of depression. J Clin Psychiatry 60(Suppl 14):3–9.
Thase ME, Gelenberg A, Kornstein SG, Kocsis JH, Trivedi MH, Ninan P, et al. 2011. Comparing venlafaxine extended release and fluoxetine for preventing the recurrence of major depression: results from the PREVENT study. J Psychiatr Res 45(3):412–420.
Thies-Flechtner K, Müller-Oerlinghausen B, Seibert W, Walther A, Greil W. 1996. Effect of prophylactic treatment on suicide risk in patients with major affective disorders. Data from a randomized prospective trial. Pharmacopsychiatry 29(3):103–107.
Tint A, Haddad PM, Anderson IM. 2008. The effect of rate of antidepressant tapering on the incidence of discontinuation symptoms: a randomised study. J Psychopharmacol 22(3): 330–332.
Tondo L, Jamison KR, Baldessarini RJ. 1997. Effect of lithium maintenance on suicidal behavior in major mood disorders. Ann NY Acad Sci 836:339–351.
Valenti M, Pacchiarotti I, Bonnin CM, Rosa AR, Popovic D, Nivoli AM, et al. 2012. Risk factors for antidepressant-related switch to mania. J Clin Psychiatry 73(2):e271–276.
van den Broek WW, Birkenhager TK, Mulder PG, Bruijn JA, Moleman P. 2006. Imipramine is effective in preventing relapse in electroconvulsive therapy-responsive depressed inpatients with prior pharmacotherapy treatment failure: a randomized, placebo-controlled trial. J Clin Psychiatry 67(2):263–268.
Vieta E, Colom F. 2011. Therapeutic options in treatment-resistant depression. Ann Med 43(7):512–530.
Vieta E, Cruz N. 2012. Head to head comparisons as an alternative to placebo-controlled trials. Eur Neuropsychopharmacol 22(11):800–303.
Vittengl JR, Clark LA, Dunn TW, Jarrett RB. 2007. Reducing relapse and recurrence in unipolar depression: a comparative meta-analysis of cognitive-behavioral therapy's effects. J Consult Clin Psychol 75(3):475–488.
Vothknecht S, Kho KH, van Schaick HW, Zwinderman AH, Middelkoop H, Blansjaar BA. 2003. Effects of maintenance electroconvulsive therapy on cognitive functions. J ECT 19(3):151–157.
Wells KB, Burnam MA, Rogers W, Hays R, Camp P. 1992. The course of depression in adult outpatients. Results from the Medical Outcomes Study. Arch Gen Psychiatry 49(10): 788–794.
Wijkstra J, Nolen WA, Algra A, van Vliet IM, Kahn RS. 2000. Relapse prevention in major depressive disorder after successful ECT: a literature review and a naturalistic case series. Acta Psychiatr Scand 102(6):454–460.
Wilkinson P, Izmeth Z. 2012. Continuation and maintenance treatments for depression in older people. Cochrane Database Syst Rev 11:CD006727.
Williams LJ, Henry MJ, Berk M, Dodd S, Jacka FN, Kotowicz MA, et al. 2008. Selective serotonin reuptake inhibitor use and bone mineral density in women with a history of depression. Int Clin Psychopharmacol 23(2):84–87.
Wilson KC, Mottram PG, Ashworth L, Abou-Saleh MT. 2003. Older community residents with depression: long-term treatment with sertraline. Randomised, double-blind, placebo-controlled study. Br J Psychiatry 182:492–497.