INTERNATIONAL JOURNAL OF PSYCHIATRY IN CLINICAL PRACTICE, 2017
http://dx.doi.org/10.1080/13651501.2017.1306082

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Pharmacological treatment of unipolar depressive disorders: summary of WFSBP guidelines

Michael Bauer[a], Emanuel Severus[a], Hans-Jürgen Möller[b], Allan H. Young[c] and WFSBP Task Force on Unipolar Depressive Disorders*

[a]Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; [b]Department of Psychiatry, Ludwig-Maximilians-University, Munich, Germany; [c]Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

ABSTRACT

Objective: Major depressive disorder (MDD) is a severe mood disorder affecting individuals of all ages and is characterised by single or recurrent major depressive episodes. Key elements of acute and maintenance treatment of MDD include pharmacotherapy, and psychological approaches such as psychoeducation and adherence monitoring.

Methods: This summary of the 'Practice guidelines for the biological treatment of unipolar depressive disorders' comprises acute, continuation and maintenance treatment developed by an international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP), and focuses on pharmacological treatment options.

Results: A variety of different antidepressants are available for the effective acute and prophylactic treatment of depressed patients. Randomised placebo-controlled efficacy studies indicate that all major classes of antidepressants are effective in acute treatment but also in preventing recurrence of depression showing about a two-fold higher relapse rate with placebo treatment. Evidence suggests that the 'newer' antidepressants have superior long-term effectiveness due to better tolerability and safety profile compared to traditional antidepressants, e.g., the tricyclic antidepressants (TCA).

Conclusions: Despite progress in the availability of different treatment options there is still a substantial proportion of patients who do not achieve full remission. Several add-on pharmacological treatment options are among the best-evidenced strategies for refractory depressed patients.

ARTICLE HISTORY
Received 12 September 2016
Revised 31 January 2017
Accepted 8 March 2017

KEYWORDS
Primary care; major depressive disorder; pharmacotherapy; guidelines

Introduction

Major depressive disorder (MDD) is a severe mood disorder affecting individuals of all ages and races and is characterised by single or recurrent major depressive episodes of at least two weeks' duration, although most episodes last considerably longer. The worldwide global burden of disease (GBD) study of the world health organization (WHO) has shown variations by country and region but patterns and trends for depressive disorders are remarkably similar worldwide. MDD can begin at any age, even in childhood and adolescence, but the mean age of onset of MDD has been estimated around the age of 30, sometimes it begins in late life. It has been estimated that 50–85% of the patients who have an episode will have another episode of major depression (Judd et al. 1998).

The prognosis for a single depressive episode that is treated according to standard procedures (involving pharmacotherapy and psychotherapy) is generally good and most patients return to normal functioning when the episode is over. However, MDD is associated with considerable morbidity and mortality when an initial episode of depression evolves into a recurrent and debilitating chronic illness with significant and pervasive impairments in psychosocial functioning. The likelihood of a recurrence increases with the number of previous depressive episodes and the severity of the current episode (Angst & Merikangas 1997; Kendler et al. 2000). Patients who already have had three episodes of major depression have a high risk (of about 90%) of having another (for other risk factors of relapse, see Table 1).

An asymptomatic recovery from MDD is associated with significant delays in episode relapse and recurrence and a more benign course of illness. Unfortunately, it has become apparent in recent years that the long-term course of unipolar MDD is not only characterised by high rates of recurrence but also dominated by prolonged symptomatic chronicity (Judd et al. 2000). Subsyndromal symptoms in the course of MDD are associated with high risk for early episode relapse and a significantly more chronic future course of illness.

This manuscript is a short summary of the 'Practice guidelines for the biological treatment of unipolar depressive disorders' containing pharmacological treatment options, and includes part 1 (acute and continuation treatment; Bauer et al. 2013) and part 2 (maintenance and long-term treatment; Bauer et al. 2015). This summary paper is not fully referenced (for details, see: Bauer et al. 2013 and Bauer et al. 2015).

Methods

Goals and target audience

These treatment guidelines were developed by an international Task Force of the World Federation of Societies of Biological

CONTACT Michael Bauer michael.bauer@uniklinikum-dresden.de Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Fetscherstr. 74 D-01307 Dresden, Germany
*WFSBP Task Force on Unipolar Depressive Disorders: Michael Bauer, Chair, Germany; Allan H. Young, Co-Chair, United Kingdom; Emanuel Severus, Secretary, Germany. The list of members is provided in the Acknowledgements section.

Table 1. Factors associated with increased risk for recurrence in major depressive disorder.

- Three or more episodes of major depression
- High prior rate of recurrence (e.g., two episodes within five years)
- Previous episode in the last year
- Residual symptoms during continuation phase treatment
- Residual subsyndromal symptoms at remission
- Concurrent dysthymic disorder ('double depression')
- Severity of episodes (includes suicidality and psychotic features)
- Longer previous episodes
- Relapse after medication withdrawal
- Concurrent coexisting substance abuse
- Concurrent coexisting anxiety disorders
- Family history of major depressive disorder in first degree relatives
- Onset prior to age 30

Psychiatry (WFSBP) and provide an update of contemporary knowledge of unipolar depressive disorders and evidence-based recommendations for their treatment (Bauer et al. 2013, 2015). The recommendations presented are based on an initial comprehensive review of all available evidence by a systematic update literature search and appraisal. The guidelines are intended for use by all physicians, particularly psychiatric specialists, seeing patients with depressive disorders. They deal primarily with biological (somatic) treatment (e.g., antidepressants). The data used for the development of the initial guidelines was collected from various international guidelines [for the latest versions of some relevant guidelines: British Association for Psychopharmacology (Cleare et al. 2015), Royal Australian and New Zealand College of Psychiatrists (Malhi et al. 2015), Canadian Network for Mood and Anxiety Treatments [CANMAT] (Kennedy et al. 2016)], apart from a systematic update search in the MEDLINE database.

Indications and concepts of treatment for major depressive disorders

Antidepressant treatment should be considered for patients who meet diagnostic criteria for depressive episode (ICD-10) or MDD (DSM-5). Guidelines differ with respect to the recommendation of antidepressants in mild depressive episodes or depression in primary care. Depending on individual characteristics and/or patient requests, antidepressant treatment might be indicated; otherwise, psychotherapeutic approaches alone may be sufficient. It should also be stressed that the clinical syndrome of major depression/depressive episode comprises a heterogeneous group of different types of depression ranging from the putatively biologically determined (formerly 'endogenous' or 'melancholic') conditions to more event-dependent (formerly 'reactive') conditions. However, in general, it has not been found useful to distinguish between these different types of depression when making (pharmacological) treatment recommendations.

The treatment of MDD requires conceptualization of acute, intermediate and long-term goals. Three phases of treatment correspond to the three stages of the illness: (1) acute therapy, (2) continuation therapy and (3) maintenance therapy (Figure 1).

The *acute phase* of therapy is the time period from the initiation of treatment to remission, which is the primary therapeutic goal. The *continuation phase* follows the acute phase to preserve and stabilise the remission. It is the phase in which the treatment is extended for a period of time in order to prevent a return of the depression. *Maintenance (prophylactic) and long-term treatment* is aimed at preventing recurrence of depression and suicide as well as to enable full and lasting functional recovery.

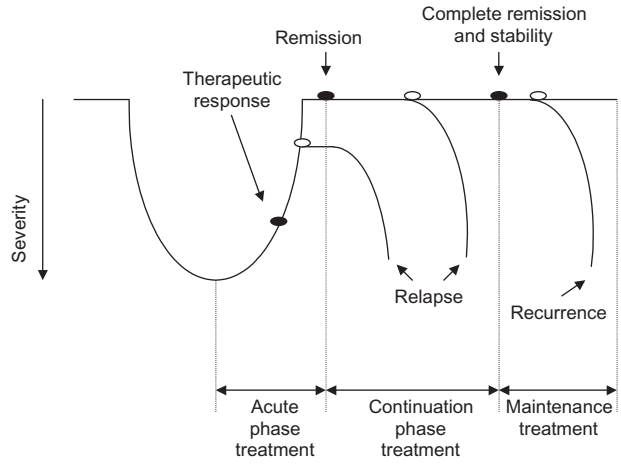

Figure 1. Major depression: phases of disease and treatment. Adapted version, original from D. Kupfer (1993).

Acute depressive episode: general treatment recommendations

For patients who meet diagnostic criteria for depressive episode (ICD-10) or MDD (DSM-5), biological treatment (pharmacological and non-pharmacological approaches) should, in general, be considered. Before treatment starts, a comprehensive treatment plan should be developed on the basis of the patient's history and experience with previous treatments, current clinical subtype, current findings and severity of illness and risk of suicide. Concurrent psychiatric and somatic disorders, non-psychiatric medications, or psychosocial stress factors should be thoroughly considered, as they can contribute to a depressive syndrome or interfere with treatment. Family history for mood disorders and familial response to treatments should be assessed. Whichever biological treatment intervention is chosen, psychiatric management should be initiated and continued throughout the treatment. This includes determining treatment plan and setting, establishing and maintaining a therapeutic alliance, monitoring and reassessing mental status including risk of suicide, reassessing the adequacy of the diagnosis, monitoring the patient's treatment response, side effects and general medical condition and educating patients and families as to the importance of adhering to treatment. Whenever possible, the patient's preferences and previous treatment experiences should be considered. If indicated (e.g., if psychotic features or suicidality co-occurs) the need for inpatient treatment in a specialised facility should be addressed.

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

Acute depressive episode: pharmacological treatment recommendations

The development of antidepressant medications has been one of the most important achievements in the treatment of major depression. Since the introduction of the first tricyclic antidepressant (TCS) (imipramine) in 1957, several different classes of antidepressants have been introduced to the pharmacotherapeutic armamentarium. The 'newer', pharmacologically more selective

Table 2. Major classes of antidepressants[a].

- Tricyclic antidepressants (TCA)
- Tetracyclic antidepressants
- Selective serotonin reuptake inhibitors (SSRI)
- Selective norepinephrine reuptake inhibitors (NRI)
- Selective serotonin and norepinephrine reuptake inhibitors (SNRI)
- Monoamine oxidase inhibitors (MAOI)
- Noradrenaline and dopamine reuptake inhibitor (NDRI)
- Melatonin receptor agonists

[a]Individual compounds see Table 3; the classification is heterogeneous, originates historically and pharmacologically.

antidepressants (e.g., the selective serotonin reuptake inhibitors [SSRI]), were primarily developed with an aim of reducing side effects and lowering toxicity in overdose. The classes of antidepressants currently available differ little in their antidepressant efficacy, all producing treatment responses of about 50–60%.

Choice of antidepressant

Antidepressants are the first-line treatments for a major depressive episode, which is moderate to severe. Depending on individual characteristics and/or patient requests, antidepressant treatment might also be indicated in mild depressive episodes, but, in many such cases, psychotherapeutic approaches alone may be sufficient.

Antidepressant medications are grouped into several classes (Table 2). The classification, historically grown since the 1950s, is a mixture of nomenclatures that take into account chemical structures and pharmacological receptor binding properties; a generally accepted uniform systematic classification has been proposed but is not yet globally accepted (Uchida et al. 2017). Factors to take into account when choosing an antidepressant are: the patient's prior experience with medication (response, tolerability and adverse effects); concurrent medical conditions and use of non-psychiatric drugs; a drug's short- and long-term side effects; toxicity of overdose in patients at risk of suicide; the physician's own experience with the medication; the patient's history of adherence to medication; history of first-degree relatives responding to a medication; patient preferences; potential budgetary constraints; availability of specific antidepressants and the license of the compound. Table 3 displays mode of action, neurochemical classification, recommended doses and therapeutic drug monitoring recommendations for antidepressants.

Comparative efficacy

No single class of antidepressants has proven to be clearly more effective or have a more rapid onset than any other, although some TCA (amitriptyline and clomipramine) and venlafaxine are slightly more effective than SSRI in severely depressed hospitalised patients. Antidepressants differ considerably in their side-effects profile, potential for interacting with other drugs and in the danger they pose when taken in overdose. Second (e.g., bupropion, maprotiline, mianserin and trazodone) and third (e.g., SSRI, SNRI and mirtazapine) generation ('newer') antidepressants are generally tolerated better than are the first generation ('older') TCA and patients are, thus, less likely to discontinue them. This may have a significant impact on 'real-life' efficacy.

The 'older' (e.g., tricyclics and tetracyclics) and 'newer' (e.g., SSRI, SNRI, mirtazapine, bupropion and agomelatine) antidepressants have, in numerous placebo-controlled studies, proved effective in treating MDD. Considering response, the placebo-verum difference was estimated to be roughly between 10% and 20% corresponding to a number needed to treat (NNT) of 5–7. The 'older' (irreversible) MAO inhibitors (e.g., tranylcypromine and phenelzine) are not considered first-line treatments. Although their efficacy is comparable to TCA, they entail the risk of potentially fatal hypertensive crisis or serotonin syndrome (see below) in patients who eat foods containing tyramine (e.g., aged cheese, aged or cured meats, soy sauce and soy bean condiments, salted fish, and red wine; see manufacturer's warning notices) or use certain medications.

The numerous tricyclics do not differ among themselves in terms of efficacy, but do show different side effect profiles. In general, there are no clinically significant differences in efficacy and effectiveness between TCA and SSRI. One meta-analysis did show evidence that TCA may be slightly more effective than SSRI in hospitalised patients and severely ill patients; however, another meta-analysis of fewer RCTs using a different methodology found that the advantage of TCA over SSRI did not reach statistical significance.

Side effects of antidepressants

Side effects vary between classes of antidepressants and to some extent between individual agents (see Table 4). SSRI are generally tolerated better than TCA and show lower rates of treatment discontinuation. SSRI are safer and have higher tolerability profiles than tricyclic and tetracyclic antidepressants, causing fewer anticholinergic side effects and cardiovascular toxicities. An agent may have a side effect profile which makes it particularly suitable for patients with specific concurrent, non-psychiatric medical conditions. For patients with coronary artery disease, for example, drugs that do not lower blood pressure or are not associated with changes in cardiac conduction (e.g., bupropion and SSRI) are preferable. Among the tricyclics, the secondary amines (e.g., desipramine and nortriptyline) have fewer side effects than do the tertiary amines (e.g., amitriptyline and imipramine).

Treatment options for the partial- and non-responding patient to initial treatment

Optimising antidepressant medication

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

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

In at least 30–40% of depressive episodes, patients will not respond sufficiently to an adequately performed first-line treatment with any chosen antidepressant. Various alternative treatment strategies have been proposed for these non- or partially

Table 3. Mode of action and recommended doses of antidepressants.

Generic name[a] (in alphabetical order)	Traditional structural classification[b]	Classification according to neurochemical action[b]	Starting dose[c] (mg/day)	Standard dose[d] (mg/day)	Plasma levels[e] (therapeutic range) (ng/mL)
Agomelatine		MT agonist	25	25–50	
Amineptine			100	200–300	
Amitriptyline[f]	TCA		25–50	100–300	80–200[l]
Amoxapine	TetraCA		50	100–400	
Bupropion[g]		NDRI	150	150–450	
Citalopram[i]		SSRI	20	20–40 (60)	
Clomipramine[h,i]	TCA		25–50	100–250	175–450[l]
Desipramine	TCA		25–50	100–300	100–300
Dibenzepine	TCA		120–180	240–720	
Dosulepine	TCA		75	75–150	
Dothiepin	TCA		25–50	100–300	
Doxepine[i]	TCA		25–50	100–300	
Duloxetine[k]		SNRI	30–60	60–120	
Escitalopram[i]		SSRI	10	10–20	
Fluoxetine[h]		SSRI	20	20–60	
Fluvoxamine[h]		SSRI	50	100–200	
Imipramine	TCA		25–50	100–300	175–300[l]
Isocarboxazid[i]			20	20–60	
Lofepramine	TCA		70	140–210	
Maprotiline	TetraCA		25–50	150–225	
Mianserin	TetraCA	§	30	60–120	
Milnacipran		SNRI	50–100	100–200	
Mirtazapine		$	15	15–45	
Moclobemide		RIMA	150	300–600	
Nefazodone			100	300–600	
Nortriptyline	TCA		25–50	75–200	70–170
Paroxetine[h,i,j]		SSRI	20	20–40 (60)	
Phenelzine[i]		MAOI	15	30–90	
Protriptyline	TCA		10	20–60	
Reboxetine		NARI	4–8	8–12	
Sertraline[h,i,j]		SSRI	50	50–150	
Setiptiline	TetraCA		3	3–6	
Tianeptine		#	12.5	25–37.5	
Tranylcypromine[i]		MAOI	10	20–60	
Trazodone			50–100	200–600	
Trimipramine[f,i]	TCA		25–50	100–300	
Venlafaxine[j]		SNRI	37.5–75	75–375	195–400[l]
Viloxazine			100	200–500	
Vortioxetine		Multimodal	5–10	10–20	

[a]Availability on the market differs considerably across countries.
[b]Abbreviations see below.
[c]Lower starting doses may be needed for older adults (>60) or patients with co-morbid medical illness (especially cardiovascular conditions; see text).
[d]Standard doses are generally lower in Japan.
[e]Only given for those antidepressants with well-established therapeutic range.
Other indications than depression (approved in some countries) or common uses.
[f]Chronic pain.
[g]Smoking cessation.
[h]Obsessive–compulsive disorder (OCD).
[i]Anxiety disorders (panic disorders, PTSD, social phobia).
[j]Generalized anxiety disorder.
[k]Diabetic and peripheral neuropathic pain, stress urinary incontinence.
[l]Recommended therapeutic range is the sum of the drug and the active metabolite.
Abbreviations: MAO-I: irreversible inhibition of monoamine oxidase (MAO); MT agonist: agonist of the melatonin receptor (MT1 und MT2); NARI: noradrenaline reuptake inhibition; NDRI: noradrenaline and dopamine reuptake inhibition; RIMA: reversible inhibition of monoamine oxidase A (MAO-A); SNRI: selective serotonin and noradrenaline reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressant; TetraCA: tetracyclic antidepressant; §: noradrenaline reuptake inhibition plus presynaptic alpha2-blockade; $: alpha2-antagonist; #: 5-HT reuptake enhancer.

responsive depressions. The major types of theoretical strategies employed after reviewing correctness of diagnosis and sufficiency of drug dosing and adherence, are (see also Figure 2):

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

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

Table 4. Side effect profiles of antidepressants[a].

Generic name (in alphabetical order)	Anti-cholinergic[b]	Nausea/gastro intestinal	Sedation	Insomnia/ agitation	Sexual dysfunction	Orthostatic hypotension	Weight gain	Specific adverse effects	Lethality in overdose
Agomelatine	−	+	−	−	−	−	−	Risk of increase of liver enzymes	Low
Amineptine	−	+	−	++	+	+	+	Risk of abuse (amphetamine-like effects)	Low
Amitriptyline	+++	−	+++	−	+	+++	+++	ECG changes[c]; may lower seizure threshold	High
Amoxapine	+++	−	+	++	+	+	+	Hyperprolactinemia	High
Bupropion	+	+	−	+	−	−	−		Low
Citalopram	−	++	−	++	++	−	−		Low
Clomipramine	+++	+	+	+	++	++	++	ECG changes[c]; may lower seizure threshold	Moderate
Desipramine	+	−	−	++	+	+	+		High
Dibenzepine	+	−	+	−	+	+	+		Moderate
Dosulepine	++	−	++	−	+	+	+		High
Dothiepin	+++	−	+++	−	+	+++	+++		High
Doxepin	+++	−	+++	−	++	+++	++		High
Duloxetine	−	++	−	++	+	−	−		Low
Escitalopram	−	++	−	++	++	−	−		Low
Fluoxetine		++		+					Low
Fluvoxamine	+	+++		+	+				Low
Imipramine	++	−	+	++	+	++	++	ECG changes[c]; may lower seizure threshold	High
Isocarboxazid	+	+	−	++	+	++	+	Hypertensive crisis[e]; risk of serotonin syndrome[f]	High
Lofepramine	+	−	+	++	+	+	+	ECG changes[c]; may lower seizure threshold	Low
Maprotiline	++	−	++	−	+	++	++	Increased seizure risk	High
Mianserin	+	−	++	−	−	+	+	Blood dyscrasia (rare)	Low
Milnacipran	−	++	−	++	++	−	−		Low
Mirtazapine	−	−	++	−	−	+	++		Low
Moclobemide	+	+	−	+	−	−	−		Low
Nefazodone	+	+	++	−	−	+	+	Inhibitory effects on CYP3A4[d]	Low
Nortriptyline	+	−	+	+	+	+	+	ECG changes[c]; may lower seizure threshold	High
Paroxetine	+	++	−	++	++	−	+	Inhibitory effects on CYP2D6[d]	Low
Phenelzine	+	+	+	++	++	++	+	Hypertensive crisis[e]; risk of serotonin syndrome[f]	High
Protriptyline	+++	−	+	++	+	++	+	ECG changes[c]; may lower seizure threshold	High
Reboxetine	−	+	−	++	+	++	−		Low
Sertraline	−	++	−	++	++	−	−		Low
Setiptiline	+	−	++	−	+	+	+		Moderate
Tianeptine	+	+	−	+	−	−	−	ECG changes[c]; may lower seizure threshold	Low
Tranylcypromine	−	+	−	++	+	++	−	Hypertensive crisis[e]; risk of serotonin syndrome[f]	High
Trazodone	−	+	++	−	++	+	+	Priapism (rare)	Low
Trimipramine	++	−	+++	−	+	++	++	ECG changes[c]; may lower seizure threshold	High
Venlafaxine	−	++	−	++	++	−	−	Hypertension	Low
Viloxazine	−	+	−	++	−	−	−		Low
Vortioxetine	−	++	−	++	+	−	−		

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

[a]These side effect profiles of antidepressants are not comprehensive and are for rough comparison only. Details of drugs used and potential cautions and interactions should be looked up in textbooks/reviews (e.g., the primary literature or the complete prescribing information available in the package insert of the drug.

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

[c]Conduct delays.

[d]Only those inhibitory effects on hepatic CYP450 enzymes are shown that are clinically relevant.

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

[f]Combination with serotonergic drugs.

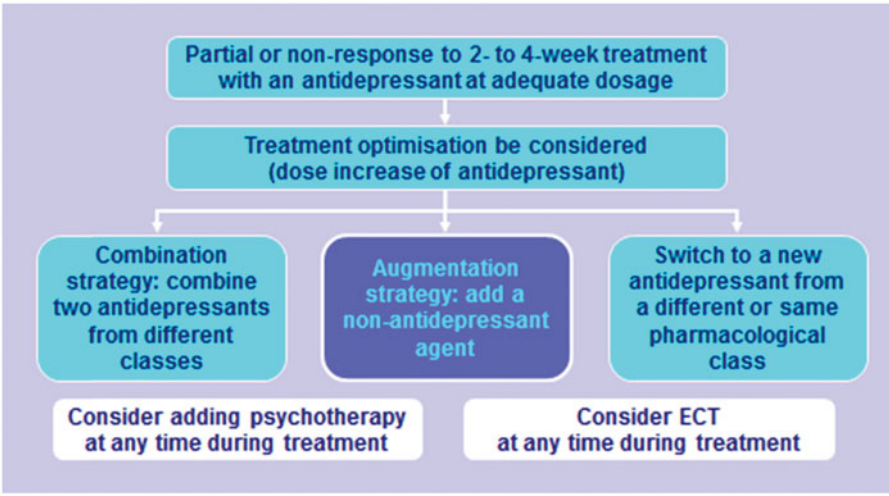

Figure 2. Therapeutic options in antidepressant failures in patients with major depressive disorder.

derived from theoretical viewpoints and are not supported by data from double-blind controlled studies. Thus, empirical data concerning the choice of the appropriate strategy are limited. Currently, no clear consensus exists on which strategy should be favoured for the non-responding patient. In the following sections, the commonly uses strategies in clinical practice will be discussed briefly.

Strategy 1: increasing (maximising) the dose the initial antidepressant

A common strategy in patients not responding to a single antidepressant is dose escalation. However, the available evidence for this approach is, at best, incomplete. For tri- und tetracyclic antidepressants, positive evidence from dose finding studies as well as from therapeutic drug monitoring exist for a dose–response relationship, which may be differ, according to the antidepressant tested. The same holds true for venlafaxine, which seems to be more efficient at higher doses; for SSRI, no such evidence exists. In fact, the available data suggest that the minimal effective dosage corresponds to a more than 80% occupancy of the serotonin transporter and that this percentage cannot be further increased by dose escalation. However, in contrast, in a recent systematic review and meta-analysis higher doses of SSRI appeared slightly more effective in MDD; these slightly increased benefits appeared to plateau at around 250 mg of imipramine equivalents (50 mg of fluoxetine) and were somewhat offset by decreased tolerability at high doses (Jakubovski et al. 2016). Regarding the irreversible MAO–inhibitor tranylcypromine, small studies indicate increased efficacy at higher doses.

Strategy 2: switching to another antidepressant (stay within monotherapy)

The potential advantage of switching to another antidepressant class is that it minimises polypharmacy, which helps prevent toxicity and negative drug–drug interactions, may lead to fewer or less severe side effects and can, therefore, improve patient adherence. Disadvantages in such a switch are a potential loss of partial efficacy by switching from initial antidepressant and the relatively long period until the second agent can develop its full antidepressive activity (delayed onset compared to augmentation or combination). However, switching to another antidepressant (intra- or inter-class) may not be superior to continuing the initial antidepressant (Bschor & Baethge 2010, consider that data reviewed are limited to switch to TCA and SSRI).

Strategy 3: combining two antidepressants from different classes

Rational antidepressant combinations take advantage of complementary mechanisms of action to confer synergistic benefits. Reasons in support of such combination treatment include avoidance of loss of partial response with initial monotherapy. Disadvantages of this strategy are the increased risk of drug–drug interactions, potentiation of side effects and drug costs. Although often applied in clinical practice, few controlled data in support of the utility and efficacy of this strategy exist. The addition of a TCA to an SSRI or vice versa, and also many other different combinations of antidepressants, have been tried with varying success. Combining irreversible MAO inhibitors with SSRI and other antidepressants which act on the serotonergic system (e.g., clomipramine and venlafaxine) should be avoided due to potentially fatal interactions (serotonin syndrome). In summary, the combination of an SSRI with an inhibitor of presynaptic autoreceptors (e.g., mirtazapine) is the best evidence-based choice in cases where monotherapy failed. The combination of venlafaxine with mirtazapine may be accompanied by worsening side effects.

Strategy 4: augmentation of antidepressants

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

Lithium

Lithium has been found to augment the therapeutic effects of a broad spectrum of antidepressants including TCA and to a lesser extent also SSRI. A meta-analysis including ten prospective studies provided firm evidence that lithium augmentation is superior to placebo in unipolar major depression, with response rates on average of 41.2% in the lithium group and 14.4% in the placebo group (Crossley & Bauer 2007). Adding lithium to ongoing antidepressant treatment is recommended in case monotherapy failed). Lithium augmentation should be administered for two to four weeks in order to allow assessment of the patient's response.

Table 5. Pharmacological augmentation strategies in major depressive disorder – selection of commonly used agents[a].

Class	Individual agent	Dose range	Level of evidence[b]
Lithium salts	Lithium carbonate	450–1200 mg/d[c]	A
Antipsychotics[d]	Aripiprazole	5–10 d	A
	Quetiapine	150–300 mg/d	A
	Olanzapine	5–20 mg/d	B
	Risperidone	1–3 mg/d	B
	Brexpiprazole	1–3 mg/d	A
	Cariprazine	1–4 mg/d	B
Thyroid hormones	Triiodothyronine (T3)	25–50 µg/d	B
	Levothyroxine (L-T4)	200–400 µg/d	C
Anticonvulsants	Lamotrigine	50–300 mg/d	B
	Carbamazepine	200–1200 mg/d, 20–40 µmol/l	C
	Valproic acid	600 mg/d	C
Dopamine agonists	Bromocriptine	7.5–52.5 mg/d	C
	Pergolide	0.25–2.0 mg/d	C
	Pramipexole	0.375–1.0 mg/d	C
Psychostimulants	Methylphenidate	18–80 mg/d	C
	Modafinil	100–400 mg/d	B
Buspirone		10–60 mg/d	C
Nutrition supplements			
Omega-3-polyunsaturated fatty acids	Eicosapentaenoic acid	0.6–4 g/d	C
	Docosahexaenoic acid	2.4 g/d	C
S-adenosyl-methionine (SAMe)		1600 g/d	C

[a]Displays only compounds not classified as antidepressants (see Table 1).
[b]Levels A–D, classification modified from WFSBP guidelines (Bauer et al. 2013) (A: good evidence from RCTs; B: moderate evidence from RCTs; C: low evidence from RCTs).
[c]Corresponds to a serum level of 0.6–0.8 mmol/l.
[d]Other atypical antipsychotics (e.g., ziprasidone, sertindole, amisupride and asenapine) have also been studied in this indication but to a lesser extent.

The recommended lithium serum target levels are 0.6–0.8 mmol/L. In case of response, lithium augmentation should be continued for at least 12 months.

Atypical antipsychotics (second generation antipsychotics)

Several double-blind controlled trials are available for augmentation with aripiprazole, olanzapine, quetiapine, risperidone, brexpiprazole and cariprazine (for recent reviews of second generation antipsychotics see Spielmans et al. 2013; Zhou et al. 2015; Wang et al. 2016; Durgam et al. 2016; Lao et al. 2016). A Cochrane review and meta-analysis reviewed augmentation with aripiprazole, olanzapine, quetiapine and risperidone. Augmentation with aripiprazole was found to be significantly more beneficial compared to antidepressant alone but caused more unwanted effects (weight gain and EPMS). The results for augmentation with olanzapine were more ambiguous and accompanied by more side effects as weight gain and prolactin increase. Quetiapine augmentation was significantly more effective compared to antidepressant monotherapy but more weight gain and sedation was found in a meta-analysis. Risperidone augmentation was significantly more effective compared to antidepressant alone but benefit was not sustained during continuation phase therapy. In addition it was accompanied by more weight gain and prolactin change from baseline. In summary, augmentation of antidepressants with quetiapine or aripiprazole represents an alternative to lithium augmentation and is recommended in case monotherapy failed. Potential unwanted effects include sedation (quetiapine), weight gain (quetiapine and to a lesser extent aripiprazole) and akathisia (aripiprazole).

Beyond for augmentation treatment, atypical antipsychotics have been studied in other indications for MDD patients. In a recent randomised placebo-controlled study lurasidone, a novel atypical antipsychotic agent, significantly improved depressive symptoms and overall illness severity in patients with MDD with mixed features (DSM-IV criteria for MDD who presented with two or three manic symptoms) (Suppes et al. 2016).

Thyroid hormones

Studies assessing the effects of thyroid hormones in treatment-resistant depression (TRD) have largely focused on T3 as the augmenting thyroid hormone. Numerous case series and at least 13 prospective trials (nine open and four controlled double-blind studies) have evaluated the use of T3. A meta-analysis did not find consistent results in favour of T3 augmentation. WFSBP recommendation: The augmentation of antidepressants with thyroid hormones appears legitimate in cases where monotherapy failed. Thyroid hormones should be administered with caution because of potential unwanted effects.

Adjunctive therapy

Interventions intended to provide complementary effects are referred to as adjunctive therapies. Pharmacological as well as non-pharmacological adjunctive therapies have been suggested for the treatment of major depression. Most commonly, tranquilisers/anxiolytics (e.g., benzodiazepines), hypnotics, sleep deprivation and exercise training are considered adjunctive pharmacological therapies. Many of these treatments may help to reduce anxiety and insomnia until full recovery of depression is achieved. It is recommended that the potential benefits of adjunctive treatment with benzodiazepines must be carefully weighed against possible harm (including sedation, psychomotor and cognitive impairment, potentiation of other central nervous system depressants and development of dependence and discontinuation syndromes). Benzodiazepines should not be administered to patients with a history of or current alcohol or drug abuse/dependence. It is also recommended that the duration of benzodiazepine administration in depressed patients should be typically restricted to a maximum period of approximately four to six weeks until the antidepressant has proved to be effective.

Sleep deprivation alone may be used to treat unmedicated depressed patients, or be started at the same time as an antidepressant medication with the goal of accelerating the response

to medication. It may also be added as a strategy to potentiate an ongoing antidepressant drug therapy.

Treatment-resistant depression

As many as 50% of non-responders to a first antidepressant trial also fail to respond to a second, different course of treatment. This residual group of patients remains depressed and do not achieve adequate relief and a satisfactory level of functioning even after two or more adequate courses of treatment. There is no universally accepted definition of treatment resistance. While many of the non-responders to initial treatment may improve with the treatment strategies that have been described above, some of these patients develop a chronic course of the illness.

It has been suggested that inadequately performed pharmacotherapy and unsystematic treatment plans may contribute to this unfavourable treatment outcome. In clinical practice, treatment-resistance frequently results from inadequate dosage and inappropriate length of treatment with antidepressants or from insufficient use of the available therapeutic repertoire in case of incomplete response. Some studies indicate that only a minority of patients labelled 'treatment-resistant' are 'absolutely' resistant, the majority of 'relative' resistors can be helped substantially by rigorous treatment approaches including a course of electroconvulsive therapy (ECT). Patients with a history of positive response to ECT may be candidates for immediate ECT when a new episode requires treatment. Repeated inadequate drug trials may be harmful to the patient and may contribute to a negative outcome of the depression. Some evidence exists that repeated drug trials per se are associated with TRD. As mentioned before, the assumption behind the development of systematic treatment approaches (algorithms) is that decreasing the variance and increasing the appropriateness of treatment strategies results in enhanced patient outcomes and avoidance of development of refractoriness (Adli et al. 2006). Treatment algorithms are key instruments aimed at improving adherence to antidepressant regimens and in optimising the execution of treatment in terms of treatment effectiveness and cost efficiency. Other reasons for treatment resistance include 'hidden bipolarity'.

Research into finding novel antidepressant therapies for TRD has evolved from investigations of antidepressants with primary mechanisms of action on the monoaminergic neurotransmitter system to augmentation agents with primary non-antidepressants, e.g., lithium, atypical antipsychotics, thyroid hormones (for an overview of commonly studied augmentation agents see Table 5), agents modulating receptors both within and outside of the serotonin/norepinephrine system. Lately, the field of antidepressant research has changed trajectories and is about to identify effective medications with primary mechanisms of action on the glutamatergic system. Specifically, recent studies demonstrated the role of glutamate-mediated neuroplasticity in the pathophysiology of mood disorders and antidepressant effects of glutamatergic agents. Ketamine, a non-selective *N*-methyl-D-aspartic acid receptor (NMDAR) antagonist, used as an anaesthetic for many years, has shown antidepressant efficacy in subanaesthetic doses within hours of administration in placebo-controlled cross-over studies for MDD. In these trials, ketamine showed rapid and robust antidepressant effects for treatment-refractory depression. Ketamine and non-ketamine *N*-methyl-D-aspartate receptor antagonists (NMDAR-antagonists) recently demonstrated antidepressant efficacy for treatment refractory depression. Single infusion of ketamine, but less so of non-ketamine NMDA-antagonists, has ultra-rapid efficacy for MDD, lasting for up to one week. Development of easy-to-administer, repeatedly given NMDA-antagonists without risk of brain toxicity is of critical importance (Kishimoto et al. 2016). Furthermore, beyond these glutamatergic modulators, anticholinergic modulators (e.g., scopolamine), opoid system modulators, anti-inflammatories (e.g., celecoxib) and botulinum toxin are in the focus of most research and some of these novel compounds are tested in pivotal studies (for a review: Papakostas & Ionescu 2015; Magid et al. 2015; Eyre et al. 2016; Garay et al. 2017).

Treatment in special circumstances

Under special circumstances, the treatment of depression needs to be modified. These circumstances include depression co-occurring with other psychiatric conditions (anxiety disorders, substance abuse or dependencies), depression in older adults, depression due to a general medical condition, depression during pregnancy and breast-feeding, and in children (Vitiello 2016; Kölch & Plener 2016).

Depressed patients with prominent symptoms of anxiety or with co-morbid anxiety disorders such as panic disorder, generalised anxiety disorder or PTSD, can be treated effectively with the SSRI or venlafaxine or TCA or MAOI, but medications should be initiated at low doses (e.g., 5 mg of fluoxetine or 10 mg of paroxetine) and increased slowly to full therapeutic doses. Rapid titration could cause a transient worsening of anxiety symptoms before anxiety and depression respond to the intervention.

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

MDD in later life is thought to be underdiagnosed and undertreated. There is insufficient data to precisely estimate the efficacy of antidepressants in patients aged 65 years and older. Also in elderly patients, continuation-phase treatment proved efficacious compared to placebo. In spite of insufficient data regarding the precise efficacy of antidepressants in the elderly, old age should not per se limit the full use of the whole spectrum of antidepressant options. Older patients are more prone to orthostatic hypotension and more sensitive to other adverse events such as cardiovascular and anticholinergic effects. Therefore, SSRI and the other/newer antidepressants are generally preferred over TCA. However, recent evidence for higher risk for unwanted outcomes with 'newer' antidepressants has to be considered and reappraised. Older patients are typically started on a lower oral dose than younger adult patients, but it may be necessary to titrate doses for effectiveness. Higher plasma concentrations for a given dose are generally found in older compared to younger individuals and doses may need to be adjusted particularly in patients with impaired renal or liver function.

Continuation and maintenance phase treatment of MDD

The long-term course of unipolar MDD is characterised by high rates of recurrence and prolonged symptomatic chronicity. The primary goals of continuation and maintenance (prophylactic) treatment are to prevent a fast relapse into depression and new episode of depression, a recurrence of the illness.

Continuation treatment

The objective of continuation treatment is to decrease the likelihood of relapse during the vulnerable period following symptomatic recovery from depression (i.e., to prevent a return of the current episode of depression). The continuation phase of

treatment is generally considered as a six-month period of time immediately following full remission. In general, patients with a history of long previous episodes are candidates for continuation-phase treatment of more than nine months. Because residual symptoms (partial remission) are strong predictors of subsequent early relapse, it is recommended to continue treatment until such symptoms have subsided. The continuation phase of treatment lasts at least six months following remission of the acute symptomatology. Treatment should be prolonged to nine months in patients with a history of long previous episodes and should continue even longer in cases of residual symptomatology and until such symptoms have subsided and in psychotic depression. In placebo-controlled continuation therapy trials, mostly with TCA, relapse rates ranged from 31% to 80% for those patients who received placebo, compared with only 0–31% of those who received active medication. Later continuation-phase studies involving SSRI, amineptine, nefazodone and reboxetine showed similar results. In these latter studies, 33–56% of the patients who did not continue active medication after stabilization (i.e., were switched to placebo) relapsed, whereas only 7–26% of those who continued on active medication relapsed.

WFSBP recommends that the same antidepressant successfully used to achieve response/remission in the acute-phase therapy should be continued at the same dose during the *continuation phase*. If no relapse occurs during continuation therapy, a gradual discontinuation of the antidepressant medication is recommended in case of first episodes. Patients should be carefully monitored during and immediately after discontinuation to ensure the stability of the remission. If tapering off results in a return of symptoms, the medication should be re-instated in the original dose for at least another six months before attempting discontinuation again. Following a successful course of acute phase lithium augmentation, combined continuation treatment using an antidepressant and lithium is superior to the combination of an antidepressant and placebo (Bauer et al. 2000).

Maintenance treatment

Even though no definite recommendation can be given as to when prophylactic therapy beyond these six to nine months of continuation therapy 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 five 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, if indicated. 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.

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. Randomised placebo-controlled studies (usually conducted one or two years during maintenance treatment) indicate that TCA, irreversible monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRI) and selective serotonin norepinephrine reuptake inhibitors (SNRI) 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., TCA). In addition they possess a more beneficial safety profile.

The maintenance treatment of patients with recurrent depression who experience recurrences during prophylactic treatment with standard agents, e.g., antidepressants and/or lithium, is one of the most challenging issues in the treatment of these disorders. However, little data from formal studies is available to guide physicians in the maintenance treatment of patients suffering from recurrences during standard prophylactic treatment. Combination therapy administering two or even three antidepressants, maybe combined with lithium are treatment options for the clinician although there is little controlled data to support such polypharmacy. With respect to lithium therapy, serum lithium levels of 0.6–0.8 mmol/L (mEq/L) are usually recommended for maintenance treatment. However, the 'optimal' serum lithium level may vary somewhat from patient to patient in the range of 0.5–1.0 mmol/L depending on individual effectiveness and side effects.

Treatment length required for maintenance treatment beyond that point is not yet fully determined. Duration may vary from three 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 five 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.

Acknowledgements

This review is dedicated to the 90th birthday of Professor Jules Angst who co-chaired this WFSBP task Force from 2002 to 2014.

WFSBP Members: Mazda Adli, Germany; Cengiz Akkaya, Turkey; Ian Anderson, United Kingdom; José L. Ayuso-Gutierrez, Spain; David Baldwin, United Kingdom; Per Bech, Denmark; Michael Berk, Australia; Istvan Bitter, Hungary; Tom Bschor, Germany; Marcelo Cetkovich-Bakmas, Argentina; Andrea Cipriani, United Kingdom/Italy; Koen Demyttenaere, Belgium; Ted Dinan, Ireland; Andrea Fagiolini, Italy; John Geddes, United Kingdom; Heinz Grunze, United Kindom; Gregor Hasler, Switzerland; Cyril Höschl, Czech Republic; Edith Holsboer-Trachsler, Switzerland; Marcus Ising, Germany; Siegfried Kasper, Austria; Sidney Kennedy, Canada; Lars

Vedel Kessing, Denmark; Parmanand Kulhara, United Arab Emirates; Raymond Lam, Canada; Rasmus W. Licht, Denmark; Chia-Yih Liu (Taiwan); Philip Mitchell, Australia; Hans-Jürgen Möller, Germany; Willem A. Nolen, Netherlands; Jong-Woo Paik, Korea; George Papakostas, USA; Yong Chon Park, Korea; A. John Rush, USA; Janusz K. Rybakowski, Poland; Allessandro Serretti, Italia; Daniel Souery, Belgium; Michael Thase, USA; Jürgen Unützer, USA; Eduard Vieta, Spain; Peter C. Whybrow, USA; Kazuo Yamada, Japan; Aylin Yazici, Turkey; Allan H. Young (Co-Chair), United Kingdom.

Disclosure statement

The preparation of these WFSBP guidelines has not been financially supported by any commercial organization.

M. Bauer has received grant/research support from Deutsche Forschungsgemeinschaft, European Commission (FP7), American Foundation for Suicide Prevention, Bundesministerium für Bildung und Forschung (BMBF). He is/has been a consultant for Janssen, Lilly, Lundbeck, Novartis, Otsuka, Servier, Takeda, and has received speaker honoraria from AstraZeneca, Ferrer Int., Servier, Lilly, Lundbeck, Otsuka and Pfizer.

E. Severus has been on the speakership bureaus of Lundbeck, Servier and Roche and has received grant support from the Bundesministerium für Bildung und Forschung (BMBF).

H.-J. Möller has received grants or is a consultant for and on the speakership bureaus of AstraZeneca, Bristol-Myers Squibb, Eisai, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Merck, Novartis, Organon, Pfizer, Sanofi-Aventis, Schering-Plough, Schwabe, Sepracor, Servier and Wyeth.

A. Young is employed by King's College London; Honorary Consultant SLaM (NHS UK). Paid lectures and advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders; no shareholdings in pharmaceutical companies; lead Investigator for Embolden Study (AZ), BCI Neuroplasticity study and Aripiprazole Mania Study; investigator initiated studies funded from AZ, Eli Lilly, Lundbeck, Wyeth; grant funding (past and present): NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK).

Funding

This study was funded by local University funds for M. Bauer.

References

Adli M, Bauer M, Rush AJ. 2006. Algorithms and collaborative-care systems for depression: are they effective and why? A systematic review. Biol Psychiatry. 59:1029–1038.

Angst J, Merikangas K. 1997. The depressive spectrum: diagnostic classification and course. J Affect Disord. 45:31–39.

Bauer M, Bschor T, Kunz D, Berghöfer A, Ströhle S, 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 Psychiat. 157:1429–1435.

Bauer M, Pfennig A, Severus E, Whybrow PC, Angst J, Möller HJ, Task Force on Unipolar Depressive Disorders. 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. 14:334–385.

Bauer M, Severus E, Köhler S, Whybrow PC, Angst J, Möller HJ, WFSBP Task Force on Treatment Guidelines for Unipolar Depressive Disorders 2015. 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. World J Biol Psychiatry. 16:76–95.

Bschor T, Baethge C. 2010. No evidence for switching the antidepressant: systematic review and meta-analysis of RCTs of a common therapeutic strategy. Acta Psychiatr Scand. 121:174–179.

Cleare A, Pariante CM, Young AH, Anderson IM, Christmas D, Cowen PJ, Dickens C, Ferrier IN, Geddes J, Gilbody S, Members of the Consensus Meeting, et al. 2015. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol (Oxford). 29:459–525.

Crossley NA, Bauer M. 2007. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. J Clin Psychiatry. 68:935–940.

Durgam S, Earley W, Guo H, Li D, Németh G, Laszlovszky I, Fava M, Montgomery SA. 2016. Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. J Clin Psychiatry. 77:371–378.

Eyre HA, Lavretsky H, Kartika J, Qassim A, Baune BT. 2016. Modulatory effects of antidepressant classes on the innate and adaptive immune system in depression. Pharmacopsychiatry. 49:85–96.

Garay RP, Zarate CA, Jr, Charpeaud T, Citrome L, Correll CU, Hameg A, Llorca PM. Forthcoming 2017. Investigational drugs in recent clinical trials for treatment-resistant depression. Expert Rev Neurother.

Jakubovski E, Varigonda AL, Freemantle N, Taylor MJ, Bloch MH. 2016. Systematic review and meta-analysis: dose-response relationship of selective serotonin reuptake inhibitors in major depressive disorder. Am J Psychiatry. 173:174–183.

Judd LL, Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Paulus MP, Kunovac JL, Leon AC, Mueller TI, et al. 1998. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. Arch Gen Psychiatry. 55:694–700.

Judd LL, Akiskal HS, Zeller PJ, Paulus M, Leon AC, Maser JD, Endicott J, Coryell W, Kunovac JL, Mueller TI, et al. 2000. Psychosocial disability during the long-term course of unipolar major depressive disorder. Arch Gen Psychiatry. 57:375–380.

Kendler KS, Thornton LM, Gardner CO. 2000. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. Am J Psychiatry. 157:1243–1251.

Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, Hasnain M, Jollant F, Levitt AJ, MacQueen GM, et al. 2016. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. pharmacological treatments. Can J Psychiatry. 61:540–560. Sep

Kishimoto T, Chawla JM, Hagi K, Zarate CA, Kane JM, Bauer M, Correll CU. 2016. Single-dose infusion ketamine and non-ketamine N-methyl-d-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. Psychol Med. 46:1459–1472.

Kölch T, Plener PL. 2016. Pharmacotherapy in psychiatric disorders of children: current evidence and trends. Pharmacopsychiatry. 49:219–225.

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

Lao KSJ, He Y, Wong ICK, et al. 2016. Tolerability and safety profile of cariprazine in treating psychotic disorders, bipolar disorder and major depressive disorder: a systematic review with meta-analysis of randomized controlled trials. CNS Drugs. 30:1043–1054.

Magid M, Finzi E, Kruger TH, Robertson HT, Keeling BH, Jung S, Reichenberg JS, Rosenthal NE, Wollmer MA. 2015. Treating depression with botulinum toxin: a pooled analysis of randomized controlled trials. Pharmacopsychiatry. 48:205–210.

Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, Hopwood M, Lyndon B, Mulder R, Murray G, et al. 2015. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 49:1087–1206.

Papakostas GI, Ionescu DF. 2015. Towards new mechanisms: an update on therapeutics for treatment-resistant major depressive disorder. Mol Psychiatry. 20:1142–1150.

Spielmans GI, Berman MI, Linardatos E, Rosenlicht NZ, Perry A, Tsai AC. 2013. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. PLoS Med. 10:e1001403.

Suppes T, Silva R, Cucchiaro J, Mao Y, Targum S, Streicher C, Pikalov A, Loebel A. 2016. Lurasidone for the treatment of major depressive disorder with mixed features: a randomized, double-blind, placebo-controlled study. Am J Psychiatry. 173:400–407.

Uchida H, Fleischhacker W, Juckel G, Gründer G, Bauer M. 2017. Naming for psychotropic drugs: dilemma and challenge. Pharmacopsychiatry. 50:1–2.

Vitiello B. 2016. Pediatric psychopharmacology. Pharmacopsychiatry. 49:226–227.

Wang SM, Han C, Lee SJ, Jun TY, Patkar AA, Masand PS, Pae CU. 2016. Second generation antipsychotics in the treatment of major depressive disorder: an update. Chonnam Med J. 52:159–172.

Zhou X, Keitner GI, Qin B, Ravindran AV, Bauer M, Del Giovane C, Zhao J, Liu Y, Fang Y, Zhang Y, Xie P. 2015. Atypical antipsychotic augmentation for treatment-resistant depression: a systematic review and network meta-analysis. Int J Neuropsychopharmacol. 18:pyv060.