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**TRENDS IN CLINICAL PRACTICE**

# Therapeutic options in treatment-resistant depression

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**Abstract**
The phenomenon of treatment-resistant depression (TRD), described as the occurrence of an inadequate response after an adequate treatment with antidepressant agents (in terms of dose, duration, and adherence), is very common in clinical practice. It has been broadly defined in the context of unipolar major depression, but alternative definitions for bipolar depression have also been suggested. In both cases, there is a remarkable lack of consensus amongst professionals concerning its operative definition. A relatively wide variety of treatment options for unipolar TRD are available, whilst the evidence is very scanty for bipolar TRD. TRD is associated to poor clinical, functional, and social outcomes. Several novel therapeutic options are currently being investigated as promising alternatives, targeting the neurotransmitter system outside of the standard monoamine hypothesis. Augmentation or combination with lithium or atypical antipsychotics appears as a valid option for both conditions, and the same occurs with electroconvulsive therapy. Other non-pharmacological strategies such as deep brain stimulation may be promising alternatives for the future. The use of cognitive behaviour therapy is recommended for unipolar TRD, but there is no evidence supporting its use in bipolar TRD.

**Key words:** *Depression, resistance, treatment*



## Introduction

The phenomenon of treatment-resistant depression (TRD) is very common in clinical practice, with 50%–60% of depressed patients not achieving full response following adequate antidepressant (AD) treatment (1,2). Some 15% of treated depressed patients achieve only partial response, whilst non-response is present in 19%–34% (3). TRD is a costly illness associated with a significant increase in both medical and psychiatric heath care costs, both direct (medical treatments, hospitalizations) and indirect (lost work and decreased productivity) for patients and family members (4,5). In fact, TRD has recently been reported to be the main factor in determining the economic burden of depression (6). TRD is usually linked to higher rates of co-morbidity, particularly with other psychiatric disorders, chronic pain, and fibromyalgia (5). On the other hand, the impact of both physical and psychiatric illness co-morbidities is much higher amongst TRD patients (1,7). TRD has been generally defined in the context of unipolar major depression, but in fact the concept can also be applied to bipolar depression (8).

Response to antidepressant treatment in mood disorders is a complex phenotype in which different factors are involved, including clinical, environmental, therapeutic, and genetic factors. Amongst clinical factors we should stress the importance of disease severity both for unipolar (9) and bipolar depression (10) and concomitant medical and psychiatric co-morbidity (alcohol abuse, anxiety, and axis II personality disorders). Other clinical variables significantly associated with TRD include suicide ideations, melancholic symptoms, early age at onset, recurrence, severity and number of episodes, number of hospitalizations, cognitive impairment, and lower functioning (10–15).

Some environmental factors related to TRD are lower socio-economic status, non-supportive

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**Key messages**

- A relatively wide variety of treatment options for unipolar treatment-resistant depression (TRD) are available, whilst the evidence is very scanty for bipolar TRD.
- Several novel therapeutic options are currently being investigated as promising alternatives, targeting the neurotransmitter system outside of the standard monoamine hypothesis.
- Augmentation or combination with lithium or atypical antipsychotics appears as a valid option for both conditions, and the same occurs with electroconvulsive therapy.

social environment, family conflicts, chronic stressors, multiple loss events, lower level of education, and social support and work dysfunction (1,16,17).

Regarding treatment-related factors, the role of inaccurate diagnosis is outstanding (18), but we should not disregard other remarkable factors such as inadequate choice of antidepressant drug, underdosing of AD treatment, poor tolerability, and poor adherence to treatment, which is common both amongst unipolar (19) and bipolar (20) patients.

Despite the lack of agreement regarding the definition of TRD, several approaches have been suggested for managing unipolar TRD, whilst the evidence is very scanty for bipolar TRD. In this review we will critically discuss the definition and outcome of TRD and focus on the suggested treatment strategies for both unipolar and bipolar TRD.

## Definition of treatment-resistant depression

TRD is typically described as the occurrence of an inadequate response after an adequate treatment with antidepressant agents (in terms of dose, duration, and compliance), among patients suffering from a depressive disorder (1). Unfortunately, beyond this broad and very general definition, we may find a dramatic lack of agreement amongst specialists which is seriously hindering the research in this field, with no less than 15 definitions suggested in the literature. A recent systematic review on the outcome of TRD (21) identified eight well designed studies on the outcome of TRD, all of them using different criteria which, of course, led to rather different conclusions amongst studies. Table I summarizes most definitions of TRD available in the literature (22-27). The European Union's Committee for Human Proprietary Medicinal Products (CHMP) defines TRD as follows: 'A patient is considered therapy-resistant when consecutive treatments with two products of different classes, used for a sufficient length of time at an adequate dose, fail to induce an acceptable effect'. Unfortunately, this very broad definition does not properly specify what 'a sufficient length of time', 'adequate dose', and 'acceptable effect' mean. On the other hand, choosing two 'products of different classes' is not supported by the literature. Despite all this, this seems to be the most frequently used definition of TRD (28), even if its utility depends on how the adequacy of a trial is defined.

TRD is not a homogeneous problem, and its definition should reflect this conceptual complexity. Hence, the definitions which include levels or stages of refractoriness may better describe this phenomenon, although it might become less straightforward and practical than monolithic definitions. Table II introduces the staging definitions of TRD presented so far (1,3,29,30).

This heterogeneity of TRD staging levels is further complicated by the use of varying definitions of treatment response, in terms of number of trials and duration and drugs. Operational definitions of AD response are usually classified into four categories: non-response (no clinically meaningful response to an adequate treatment), partial response (typically defined as a greater than 25% but less than 50% decrease in depression assessment scales), response (defined as a 50% or greater decrease in scores with a final HAM-D score of 15 or less), and remission (absence of depressed symptoms or the presence of minimal residual symptoms and return to full psycho-social functioning) (7,31). There is increasing awareness that those definitions of response and remission are overly broad and that one single time point should not be enough to qualify for such strong clinical words as 'response' and 'remission'. Moreover, we may also need to clarify the concept of *adequacy* of a specific treatment, in terms of dose, duration, and outcome definition. Considerable international debate has focused on what constitutes an 'inadequate response' which leads to treatment-resistance definition. Unfortunately, the literature does not provide yet an unequivocal description of 'inadequate response', as different definitions of treatment adequacy (in terms of dose, titration, and duration) and response to treatment (11) have been used, affecting the inter-study reliability. In terms of dosage, a current consensus is that the maximum tolerated dose should be used, according to specific dosage recommendations (1,32). In terms of duration of AD trial, although most of definitions of adequate treatment length derived from randomized

Table I. Definitions of unipolar and bipolar treatment depression.

| Definition | Reference |
|---|---|
| Treatment-resistant unipolar depression: | |
| Poor response to an adequate treatment trial and a score of above 15 on the 25-item Hamilton Rating Scale for Depression (HRS-D) | Nierenberg and Amsterdam, 1990 |
| Failure to respond to between two and six standard antidepressant treatments | Dunner et al., 2006 |
| Failure to respond to a standard antidepressant treatment and HRS-D scores above 18 | Shergill et al., 1999 |
| Treatment-resistant bipolar depression: | |
| Depression without remission despite two adequate trials of standard classes of ADs (at least 6-week adequately dosed trials), with or without augmentation | Sachs, 1996 |
| Depression that failed to respond to a trial with lithium at serum levels of at least 0.8 mmol/L for 6 weeks | Yatham et al., 2003 |
| The same criteria used for unipolar TRD, but adding to the definition the failure to respond to mood stabilizers as well as antidepressants | Gitlin, 2006 |
| Bipolar TRD when there is a failure to reach a HAM-D-17 score less than 17 after at least two adequate consecutive AD trials | Mendlewicz et al., 2010 |

controlled trials (RCTs) are 6 weeks, it has been suggested that for TRD the AD trial should be prolonged to at least 10 weeks (12 weeks in elderly patients). In terms of outcome definition the more traditional definition of treatment resistance has focused on *response*. Besides the definition of adequacy, another important issue to settle TRD definition is the *number* of failed adequate antidepressant trials that we need in order to diagnose TRD. Answers from the literature are again not univocal, and several and different criteria for the number and type of previous failed trials needed to define a diagnosis of TRD have been used in available studies, ranging from a failure to respond to one adequate trial of a single antidepressant for a minimum of 4 weeks to a failure of at least one trial of electroconvulsive therapy (ECT) (28). The same authors in their systematic review of RCTs on treatment of TRD confirmed this heterogeneity by concluding that no consensus criteria exist for the ascertainment of TRD, and studies diverge both conceptually and methodologically (within diagnostic evaluation tools, terminology, definition of TRD, evaluation of the adequacy of previous treatments, outcomes, and patients' adherence).

This overall lack of consensus on criteria for TRD definition across clinical studies causes a great variation in rates of TRD across studies; TRD would be the case for up to 30% of depressive episodes adequately treated with first-line antidepressant therapy (33), but if TRD is more widely defined as absence of remission this rate could rise up to 60% (34).

However, despite all the above-mentioned, we could state that controversy and lack of agreement relate more to researchers' needs for an operational definition of TRD, whilst in clinical practice we would advise to use the European Union's Committee for Human Proprietary Medicinal Products (CHMP) definition together with a practical approach to length of treatment and effect provided by each psychiatrist' own clinical experience.

The definition of TRD is far from being clearer in the case of bipolar depression. Moreover, despite TRD being particularly common in bipolar disorder, the definitions of bipolar TRD are scanty and no better than those in the unipolar field. The definition of bipolar TRD should consider the existing clinical and therapeutic differences between bipolar and unipolar depression (8) and should also refine their outcomes (35).

Current criteria for defining resistant bipolar depression are inadequate, the term of resistant bipolar depression has been largely neglected, and there is a need for adequate operational criteria. Table I presents some of the suggested definitions of bipolar TRD (10,36-38). However, since bipolar depression is clinically and therapeutically distinct from unipolar, it is appropriate in the definition of resistance to take into consideration the substantial differences between the two conditions, in terms of dimensional, phenomenological, and clinical features. On the other hand, newer definitions of bipolar TRD should include resistance to some atypical antipsychotics that have recently shown efficacy in the treatment of bipolar depression, such as quetiapine (39-45), or the combination of an atypical antipsychotic and an antidepressant, as in the case of olanzapine plus fluoxetine (42,43). However, even the latest definitions of bipolar TRD are somehow limited to 'antidepressant resistance' rather to resistance to the other compounds that have shown efficacy.

A systematic and more comprehensive attempt to define bipolar TRD depression has recently been suggested by Pacchiarotti and colleagues (8) in a

Table II. Staging methods for the definition of treatment-resistant depression (TRD).

| Thase–Rush treatment-resistant depression (TRD) staging method (Thase and Rush, 1997) | | Group for the Study of Resistant Depression (GSRD) (Souery et al., 2007) | | Massachusetts General Hospital Staging Method (Fava, 2003) | | STAR*D study (Rush et al., 2006) | |
|---|---|---|---|---|---|---|---|
| Stage 1 | Failure of at least one adequate trial of one major class of antidepressant | Stage A | Non-responders to: (specify) TCA, SSRI, MAOI, SNRI, ECT, other non-response to one adequate antidepressant trial.<br>Duration of trial: 6–8 weeks | Stage 1 | Non-response to each adequate trial of marketed antidepressant (at least 6 weeks) and generates an overall score of resistance | Level 1 | Failure to respond to one antidepressant treatment. Presence of residual symptoms with one antidepressant treatment ('Sub-syndromal level') |
| Stage 2 | Failure of an adequate trial of at least two distinctly different classes of major antidepressants | Stage B | Treatment-resistant depression (TRD).<br>Resistance to two or more adequate antidepressant trials. Duration of trial:<br>TRD1: 12–16 weeks; TRD2: 18–24 weeks; TRD3: 24–32 weeks; TRD4: 30–40 weeks; TRD5: 36 weeks–1 year | Stage 2 | Optimization of dose, optimization of duration, and augmentation/combination of each trial increase the overall score | Level 2 | Failure to respond to two consecutive antidepressant treatments |
| Stage 3 | Stage 2 plus failure of a third class of antidepressant, including a tricyclic antidepressant | Stage C | Chronic refractory depression: Resistance to several antidepressant trials, including augmentation strategy.<br>Duration of trial: at least 12 months | Stage 3 | ECT | Level 3 | Failure to respond to three consecutive antidepressant treatments |
| Stage 4 | Stage 3 plus failure of a an adequate trial of a MAOI | | | | | | |
| Stage 5 | Stage 4 plus failure of a an adequate course of ECT | | | | | | |

ECT = electroconvulsive therapy; MAOI = monoamine oxidase inhibitor; SNRI = serotonin and norepinephrine re-uptake inhibitor; SSRI = selective serotonin re-uptake inhibitor; TCA = tricyclic antidepressant.

recent systematic overview where the authors suggest a redefinition of resistant bipolar I and II depression, applying an 8-week period as the time needed for resistance to be defined. The authors defined as *resistant bipolar I depression* a depressive episode within bipolar disorder that fails to reach remission with adequately dosed lithium (0.8 mEq/L in the plasma), or with other adequate on-going mood-stabilizing treatment, plus lamotrigine (50–200 mg/day), or with full dose (600 mg/day) of quetiapine as monotherapy. For *resistant bipolar II depression*, the authors suggested the following definition: a depressive episode within bipolar II disorder that fails to reach remission with adequately dosed lithium (0.8 mEq/L in plasma), or other adequate on-going mood-stabilizing treatment, plus lamotrigine (50–200 mg/day), or with a dose range of 300–600 mg/day quetiapine as monotherapy. This group also proposes different degrees of severity or resistance, based on the failure to respond to a defined therapeutic algorithm (for more details see Pacchiarotti et al. (8)), measuring the degree of resistance from *refractory bipolar I/II depression* (depression persists after steps 1 and 2), *intractable bipolar I/II depression* (persistence of depression after step 3), to *involutional bipolar I/II depression* (depression persists after step 4). The outcome to be met in each step of the proposed algorithm is the currently accepted definition of remission (44,45), and the number of failed trials to be considered in the definition is one for each step.

## Course and outcome of treatment-resistant depression

The poor definition of TRD is hindering the reaching of univocal conclusions regarding its outcome (21). However, there is evidence that TRD would be associated to longer duration and greater severity (46). More than 50% of patients affected by TRD will not reach recovery (47) or will relapse (48). In a 5-year follow-up of 35 patients who had not recovered from depression over the previous 5 years, the overall rate of recovery was 38%, with a year-on-year probability of recovery of around 10% (47). Even with patients defined as a 'moderately treatment-resistant group'—those who failed to respond to 2–6 antidepressant treatments—the 1- and 2-year remission rates under naturalistic treatment condition were 3.6% and 7.8%, respectively (49).

Readmission would be the case for almost 70% of cases (27). Even when we consider the worst possible outcome—premature death—the rates would be as high as 32% in a 7-year follow-up (27). Another study reports slightly lower mortality rates: 13% over an 8-year period (26).

The outcome of TRD is obviously linked to its definition that modifies the severity of the sample across different studies. However, large studies, such as the STAR*D, report that poor outcome would be usually linked to the presence of residual symptoms and number of treatment failures (25,50), and this is supported by other studies reporting higher relapse (76% versus 25%) or recurrence rates (56% versus 42%) of TRD patients with and without sub-syndromal symptoms (51,52). However, these differences disappeared in the long term. Fekadu and colleagues (53) in a recent study found that the overall rate of relapse would rise with each successive step of treatment trial—55.3% after step 2, 64.6% after step 3, and 71.1% after step 4—indicating a highly significant linear trend. TRD is actually associated to poor social outcome, particularly in those patients who have residual symptoms, who were more likely to have longer periods with impairment in occupational functioning and worse social adaptation (49,52). Amongst the factors linked to TRD good prognosis, it is worth mentioning initial responsiveness to lithium (22), lack of previous hospitalizations (26), and shorter duration of illness (47).

In bipolar depression TRD would go along with higher rates of short-term non-response, switch to mania, cycle acceleration and rapid cycling, tolerance to therapeutic effect of drugs and of depressive relapse after discontinuation, compared with patients with unipolar depression (54). Atypical depression may be a further source of treatment resistance in bipolar patients (55).

## Treatment options for unipolar TRD

### *Pharmacologic strategies*

Pharmacotherapy strategies include optimization of current treatment, combination of different antidepressants, switch to another antidepressant, and augmentation of the antidepressant with a drug of another class.

It is worth mentioning some stepwise treatment algorithms that, so far, have proven to be acceptable for patients, although their implementation may be sometimes complex as they should be embedded in a specialized TRD-management setting (56,57). Amongst the successfully tested treatment algorithms, it is worth mentioning the German Algorithm Project (58) and the Texas Medication Algorithm Project (59). For an exhaustive review on the efficacy of treatment algorithms for unipolar depression see Adli et al. (57).

*Characterization of first-step treatment*

Adequately recording the failure of first-step treatment is crucial in the management of non-responsive depressed patients. This would help the clinician to establish whether the prescribed dose of antidepressant was adequate and taken for a sufficient duration, if the patient's adherence to medication was adequate, or the failure was due to lack of tolerability or to other factors. A further important consideration is the primary diagnosis and clinically relevant characteristics (e.g. subtypes of depression) and co-morbidity (psychiatric and medical illnesses) which may affect a correct therapeutic intervention. It is not uncommon that some alleged unipolar TRD would actually be misdiagnosed cases of bipolar depression (60); the differential diagnosis could be made paying special attention to some clinical presentations typically belonging to the bipolar signature, such as family history of bipolar disorder, predominance of behavioural symptoms, more severe diurnal mood variation, morning worsening, lability of mood and derealization, psychosis, melancholic symptoms, psycho-motor retardation (particularly linked to bipolar type I), and 'atypical' symptoms (61). The Mood Disorder Questionnaire (62) has also shown its usefulness to differentiate unipolar TRD from bipolar disorder (63).

On the other hand, the phenomenon of pseudoresistance should also be screened. This typically refers to non-response to inadequate treatment, in terms of duration/dose of the antidepressant treatment in patients who can present with poor adherence to medication or certain pharmacokinetic factors (use of concomitant metabolic inducers, rapid/fast metabolism). The use of standardized instruments such as the Antidepressant Treatment History Form (ATHF) has been recommended in order to record previous failed trails (64).

*Optimization strategies*

Optimization (of dose or treatment duration) involves firstly ensuring that the current medication is being used for a sufficient duration, at adequate dosage, and with maximal adherence of the patient. Because of the wide interindividual variation in pharmacokinetics and pharmacodynamics, finding the best AD dose for each patient is not easy. Dosage optimization can entail either a dosage decrease, if adverse effects outweigh any therapeutic effects, or a dosage increase, if a therapeutic effect has not yet been achieved. Despite a dose increase being the most common and apparently intuitive strategy to deal with non-response and, in fact, the most mentioned strategy, for instance, in a survey of UK psychiatrists (45%), followed by switching (32%) (65), the evidence behind this strategy is far from being solid. A systematic review on the efficacy of optimization strategies for unipolar depression revealed that high-dose antidepressant treatment of patients refractory to medium-dose treatment is recommended for tricyclic—but not SSRI—antidepressants (66). As poor adherence may play a role in some TRD patients, simple strategies to deal with this phenomenon—such as involving a caregiver to become responsible for the adherence, if the patients agrees—might also lead to good results and be a very basic first step of optimization. Accordingly, the use of systematic therapeutic drug monitoring is a valid and feasible alternative to optimize treatment, both by ensuring adherence and therapeutic treatment serum levels (67).

*Combination therapy*

The use of at least two antidepressants with well established efficacy is defined as combination therapy in TRD. Usually this approach is used when the AD monotherapy has failed, and the rationale behind it is that two ADs with different mechanisms of action may have complementary and synergic effects (68). Combination strategies have the same advantages and disadvantages as augmentation therapy (69). In one of the first well designed randomized trials on combination therapy, even keeping in mind the modest sample size, Davidson et al. (70) found that the combination of phenelzine and amitriptyline ($n = 8$) was less effective than ECT ($n = 9$). In another randomized trial, Fava et al. (71) studied 41 patients who had not responded to an 8-week trial of 20 mg of fluoxetine. Patients were randomized into three groups corresponding to optimization therapy (up to 60 mg of fluoxetine), augmentation with lithium, or combination with desipramine, with no significant differences at the end of the 4-week trial. However, due to the lack of a placebo arm, it is hard to tell if the three interventions failed or were somehow efficacious. The same study suggested that partial responders may respond better to optimization strategies. Later replications of this study found very similar results (72,73). Some modestly (superiority of the combination versus monotherapy not reaching statistical significance but higher response rates for the monotherapy) positive results come from studies on fluoxetine and desipramine (74) and for fluoxetine with trazodone (75). Maes at al. (76) reported the superior efficacy of the combination fluoxetine plus mianserin against fluoxetine optimization strategy. The described combination was as efficacious as an augmentation strategy (fluoxetine

plus pindolol). The mianserin-fluoxetine combination was also reported to be more efficacious than fluoxetine or mianserin monotherapy on fluoxetine-resistant patients, in a 6-week randomized trial (77). In a 5-week randomized trial, Licht and Qvitzau (78) found no benefit of adding mianserin (30 mg/day) to sertraline (100 mg/day) over sertraline (100 mg/day) monotherapy.

One open-label (79) and one randomized clinical trial (80) support the addition of mirtazapine to the existing treatment for TRD patients, although other studies, including the STAR*D, do not support this finding.

In another STAR*D study, the authors did not find any difference regarding remission rates between tranylcypromine and the combination of venlafaxine and mirtazapine on a TRD sample, although the latter strategy was more accepted due to its superior tolerability (81).

The use of the combination with a monoamine oxidase inhibitor (MAOI) has been studied in four open-label trials: Berlanga and Ortega-Soto (82) found that the combination of isocarboxazide and amitriptyline was safe, efficacious, and was preferred to monotherapy in 6 of 12 patients followed for 3 years. Konig and Wolfersdorf (83) reported a response rate of 50% of patients on the combination of moclobemide and tricyclic or tetracyclic antidepressants. Joffe and Bakish (84) reported response in 8 out of 11 TRD patients treated with moclobemide and sertraline or fluvoxamine. Hawley et al. (85) treated 50 TRD patients with moclobemide and paroxetine or fluoxetine for 6 weeks. The combination therapy was efficacious but hard to tolerate due to side-effects.

The addition of clomipramine to MAOI or fluoxetine appears to be more efficacious than these drugs in monotherapy, although the tricyclic antidepressant (TCA)–MAOI combination is associated with more adverse events, including several cases of serotonin syndrome (86).

Despite its increasing popularity, the combination with bupropion is understudied, with only two open-label reports: Lam et al. (87) studied 61 TRD patients who after failing a 6-week trial of citalopram or bupropion were treated for a further 6 weeks by switching to the other medication or by a combination of both medications. Although response rates favoured the combination, results did not reach statistical significance. In another open series, 14 out of 25 (56%) patients were reported to respond to the combination of bupropion and an SSRI (fluoxetine, sertraline, paroxetine) or SSNRI (venlafaxine).

Four open studies report some utility for the combination of reboxetine and SSRI or SNRI (88–91).

*Switching therapy*

Switching strategies include the change to another agent which can be either within or between antidepressant classes. This approach may be consequent to the lack of a satisfactory response or the presence of significant and intolerable side-effects. Switching one drug to another may have the advantage of improving adherence of the patient, fewer side-effects, and improved response, but it carries the risk of withdrawal symptoms, time-lag between initiation of the new drug, and the reluctance of the patient to take a new drug (7). The most commonly performed strategy is switching within the same class (i.e. SSRI to another SSRI) (1), which is relatively quick and has the advantage of the cross-tolerability of drugs. Switching to a different class of ADs is another option, with some evidence showing a modest advantage in remission rates when switching patients with SSRI-resistant depression to a non-SSRI (bupropion, mirtazapine, venlafaxine) versus within-class switches provided by a comprehensive meta-analysis (92). However, the number needed to treat to find some advantage was possibly too high ($n = 27$) to justify this strategy in regular clinical practice. Some data showed that switching to fluoxetine in patients non-responding to sertraline or sertraline and imipramine (93) showed improving efficacy after the switch, as well as switching to mirtazapine from an SSRI (94). Venlafaxine and paroxetine switching in patients non-responding to prior two antidepressant trials showed improved efficacy in a double-blind trial (95). However, a recent meta-analysis showed a lack of overall benefits of the switching strategy compared to continuing the initial antidepressant (96), and, moreover, data indicated that if there was any benefit it could be due to longer treatment duration.

*Augmentation therapy*

Augmentation is defined as the addition of a non-AD drug to enhance the effect of a current AD. Usually this approach is used for patients with an initial partial response to an AD, for whom a second non-AD drug may carry some benefits, such as rapid onset of action, enhanced efficacy, and the absence of withdrawal symptoms. On the other hand, augmentation can include drug–drug interactions, increased costs, and may affect patient adherence because of the polypharmacy. Electroconvulsive therapy, lithium augmentation, and thyroid augmentation were recommended as treatment options in the World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of

Unipolar Depressive Disorders (97,98), but most recently a favoured approach is augmentation with antipsychotics, namely aripiprazole or quetiapine. The most common studied strategy is lithium augmentation (99–102). Some studies showed a substantially higher efficacy of lithium augmentation versus placebo in patients treated with TCAs (103), but other studies found no clear advantage of lithium augmentation of fluoxetine (72,104). Two meta-analyses on the efficacy of acceleration and augmentation of antidepressants with lithium showed modest evidence for the former strategy and consistent evidence on the efficacy of lithium augmentation (odds ratio $>3$ favouring this strategy) (105). Lamotrigine, approved by the FDA for the maintenance treatment of bipolar depression, has got some evidence in TRD in retrospective studies (106,107), but due to negative placebo-controlled trials data are not supportive of its role in the treatment of TRD (108,109). Thyroid hormone supplementation (triiodothyronine (T3) and thyroxine (T4)) has been studied as an augmentation strategy of TCA (110,111), but data are lacking for SSRIs. A randomized controlled study did point at some mild improvement in the MADRS using a buspirone augmentation strategy: although at the end-point there was no significant difference between treatment groups, the most severe patients showed a significantly greater reduction in MADRS score in the buspirone group as compared with placebo (112). Mirtazapine augmentation is also supported by some positive evidence (79,80). It may be considered as a reasonable choice as an augmentation agent for TRD, but larger controlled trials are needed. As mentioned before, an increasingly common approach is augmentation with atypical antipsychotics. Aripiprazole showed positive results in three double-blind, placebo-controlled trials as an augmentation strategy for TRD (113–115), obtaining a FDA indication for adjunctive treatment of major depression. It can be considered an adequate augmentation strategy. Quetiapine extended release is approved in the US and Europe for the adjunctive treatment of major depression in patients receiving antidepressants. The indication implies the use of quetiapine in patients with insufficient response, which is not the same as TRD. Olanzapine augmentation has been evaluated in combination with fluoxetine (olanzapine-fluoxetine combination (OFC)), with positive results in one study (116) and in one of the two pooled studies (117), but with negative results in three other studies (117–119), reaching FDA approval for the acute treatment of TRD as a fixed combination, rather than augmentation. Further data directly comparing olanzapine to other augmenting agents with more benign side-effect profiles are needed in order to clarify its clinical implications as an augmentation agent for TRD (120). Risperidone showed both positive (121,122) and negative results (123,124). As a consequence of this, it may be considered as an off-label augmentation option but not as a first-line choice. Ziprasidone does not appear to have a role as an augmentation option, and no data are available on the augmentation efficacy for paliperidone, iloperidone, and asenapine. Two recent meta-analyses on the use of atypical antipsychotics for augmentation strategies in TRD have found that adjunctive antipsychotics, with no differences between agents, were all significantly more effective than placebo in response and remission rates (92,125), even if patients receiving antipsychotic augmentation were more likely to discontinue due to side-effects than those receiving placebo (weight gain, metabolic syndrome, neuromotor side-effects). A growing number of studies report the efficacy of pro-dopaminergic drugs, including dopamine receptor agonists, for major depression (126). Several studies have reported that dopamine receptor agonists (bromocriptine, pergolide, pramipexole, and ropinirole) are effective for stage 1 major depression that fails to respond to at least a single adequate conventional antidepressant treatment trial (127–131), but the clinical efficacy of dopamine receptor agonists for stage 2 treatment-resistant major depression has not been assessed. A pilot prospective, open study was undertaken by Inoue and co-workers (132) to investigate the efficacy and safety of pramipexole in patients with stage 2 TRD, suggesting that the addition of pramipexole to antidepressant treatment may be effective and well tolerated. Controlled data for stimulant augmentation for TRD are negative, despite their documented euphorigenic effect. Two studies on the extended-release methylphenidate in TRD found no separation from placebo in overall response and remission rates (133,134). The same results come from studies on atomoxetine, which did not separate from placebo in patients partially responsive to sertraline (135). A new stimulant agent, modafinil, showed augmentation efficacy in improving depression in TRD patients with significant sleepiness and fatigue, although its initial efficacy in improving depressive symptoms in general was not sustained (136,137). The pindolol augmentation was one of the past great hopes for treating TRD (138), but some studies failed to replicate this finding (139). One recent study described acceleration and enhancement of efficacy with pindolol administered together with SSRIs on TRD patients (140), but other studies (141) do not support its use. A third group of studies state that pindolol can accelerate the antidepressant action of SSRI but would not have marked efficacy on TRD (142).

*Future pharmacologic options*

Melatonin receptor agonists, such as melatonin and agomelatine, have got antidepressant effects but, as TRD patients have been excluded from studies, no conclusive data exist up to now on the efficacy of these compounds in the treatment of TRD (143,144). Preliminary positive data exist on augmentation therapy with some drugs that affect the acetylcholine receptor (AChR), such as intravenous scopolamine (145), and mecamylamine (146). Perospirone, a dopamine D2 and 5-HT2A receptor antagonist and a partial 5-HT1A receptor agonist, has shown some efficacy as an augmentation strategy, but more research is needed to confirm its usefulness (147). Other antipsychotic agents, such as asenapine or cariprazine, may have some potential as augmenting agents too. An emergent interest in the role of glutamate function in psychiatry led to studies on the role of N-methyl-aspartate (NMDA) receptor drugs in the treatment of TRD, with disappointing results for memantine (148), some positive preliminary results for ketamine (149), for CP-101,606 (an NR2 subunit-selective NMDA antagonist) (150), and for riluzole (151). The antiviral and anti-Parkinsonian drug amantadine has also shown efficacy in a preliminary study as an add-on to imipramine (152).

*Non-pharmacologic strategies*

Non-pharmacologic strategies offer additional treatment option for TRD, including psychotherapy, ECT, transcranial magnetic stimulation (TMS) or repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS).

Electroconvulsive therapy (ECT) is a well established treatment of unipolar depression and is probably more effective than drug therapy (153). ECT has showed benefits superior to those of drug-switching or augmentation strategies in depression (154) and superior to paroxetine in TRD patients (155). It has been demonstrated to be highly efficacious in severely treatment-resistant depressive disorders, with more than half of patients achieving remission (156). One alternative to ECT is magnetic seizure therapy (MST), a form of convulsive therapy in which magnetic fields are used to induce therapeutic seizures (157). In their open-label study Kayser et al. (158) tested the hypothesis that MST was associated with clinically significant antidepressant effects in TRD patients randomly assigned to receive either MST or ECT as an add-on therapy to a controlled pharmacotherapy. Antidepressant response was statistically significant in both treatment groups, and the conclusion was that MST may be a potential alternative to ECT if efficacy and safety are validated in larger clinical trials.

Vagus nerve stimulation (VNS) has been approved by the FDA for the long-term management of TRD on the basis of open trials (159–161) and a RCT (162). The rationale for the use of VNS as a long-term treatment in patients with chronic depression has been based on clinical findings and on neuroimaging findings in both epilepsy and depression patients showing alterations in medial and prefrontal limbic regions associated with neurotransmitters that have a role in anticonvulsive actions (163,164). VNS uses an implanted stimulator that sends electric impulses to the left vagus nerve via a wire lead implanted under the skin. Proposed mechanisms to explain how vagal nerve stimulation modulates mood include alteration of norepinephrine release by projections of solitary tract to the locus coeruleus, elevated levels of inhibitory GABA related to vagal stimulation, and inhibition of aberrant cortical activity by reticular system activation. Results from naturalistic studies assessing the antidepressant effect of VNS after 12 months of active treatment in patients with TRD have suggested an improvement in depressive symptoms (165–167), but the limited sample size and the lack of control group make these results difficult to interpret. In a recent 2-year open-label naturalistic follow-up by Bajbouj et al. (168), assessing the efficacy and safety of VNS in TRD patients, a clinical long-term response and a benign adverse effect profile was detected, suggesting that VNS treatment in addition to medication can offer the possibility of meaningful and sustained clinical benefit for patients who have not achieved satisfactory response with conventional treatment.

Transcranial magnetic stimulation (TMS) (single or paired pulse TMS), recently approved for the treatment of major depression by the US Food and Drug Administration, and its variant repetitive transcranial magnetic stimulation (rTMS) (repetitive TMS with longer-lasting effects) have got mixed results, but a recent meta-analysis showed a clinically significant efficacy in depression (169,170). It is a non-invasive method to cause depolarization in a specific part of the brain by using electromagnetic induction to induce weak electric currents using a rapidly changing magnetic field. A substantial research effort over the past 15 years has focused on the development of rTMS as a potential treatment alternative for patients with TRD (171), including numerous clinical trials (172–177), showing greater antidepressant efficacy of active rTMS, confirmed in several positive meta-analyses (178–180). In their 4-week randomized trial of transcranial magnetic stimulation in TRD (181), Fitzgerald and colleagues

determined the efficacy of low-frequency right rTMS to the dorsolateral prefrontal cortex (DLPFC) in a total of 219 patients with treatment-resistant depression and found that slightly more than 50% of the patients achieved clinical response criteria. It requires daily treatment for 4–6 weeks, and this limits its availability for patients. The accelerated repetitive transcranial magnetic stimulation (aTMS) may be a valid alternative, with all treatments being delivered over a few days, which has significant advantages in terms of access and patient acceptance. In a recent study, Holtzheimer and colleagues (182) tested the efficacy of aTMS in depressed patients not responding to at least one antidepressant medication. They demonstrated an excellent safety profile with efficacy for aTMS comparable to that achieved in daily rTMS in other trials. Recent results from a double-blind, randomized, sham-controlled trial would support the use of rTMS in combination with SSRI (183). Preliminary data from a naturalistic trial on high-frequency rTMS as an augmenting strategy also supports is use (184).

Deep brain stimulation (DBS), approved by the FDA as a treatment for movement disorders, appears to be a major advance in the treatment of TRD (185), although still at the research stage. It is a surgical treatment involving the implantation of brain pacemaker which sends electrical impulses to specific parts of the brain, directly changing brain activity in a controlled manner. The stimulator is placed under the skin, usually below the clavicle, and connecting wires are run under the skin to the stimulating electrodes in the brain (usually in the basal ganglia and in cingulate gyrus), in both low-frequency right-sided and high-frequency left-sided stimulation over the DLPFC, with some evidence suggesting that the right-sided low-frequency stimulation may be a first-line treatment alternative in resistant depression (186). In a recent systematic review by Lakhan and Callaway (187), positive results from studies on TRD patients were reported (189–193). Despite being an expensive treatment and not entirely without risks, DBS is a very promising new development for the treatment of severe treatment-resistant depression.

Some studies have shown that adding cognitive behaviour therapy (CBT) to medication for TRD may be beneficial in reducing depressive symptoms. For example, Thase et al. (194) compared the effectiveness of CBT and medication as second-step strategies for patients with an unsatisfactory response to an initial trial of AD medication (citalopram), reporting similar response and remission rates between patients who received CBT (either alone or in combination with citalopram) and those who received only medication. Scott et al. (195) compared medication management alone to CBT plus medication management, reporting that patients receiving combination had better psycho-social functioning than did those who received medication management alone. In a recent study Matsunaga and colleagues (196) examined the efficacy of adding CBT to treatment with medication for improving both the depressive symptoms and the social functioning of TRD patients, showing that CBT combined with medication for patients with TRD resulted in significant improvement in both the depressive symptoms and the social functioning of the patients and that improvement was maintained after a 1-year follow-up.

## Treatment options for bipolar TRD

Clinicians have few evidence-based options for the management of bipolar depression (197) and even fewer for treatment-resistant bipolar depression. To date, relatively few studies have examined the next-step treatment strategies for bipolar TRD, and no clear guidelines or unequivocal algorithms exist in order to inform clinicians on what to do when the first approved therapies fail (198,199).

Although research on optimal treatments for bipolar depression has been increasing, a lack of a sufficient database and disagreements about the classic treatment of bipolar depression have precluded a consensual treatment algorithm for treatment-resistant bipolar depression (200), and well designed studies on bipolar TRD still are lacking. As a general rule, the management of bipolar TRD includes the same operational steps as in unipolar TRD, with different treatment options. Strategies include optimization of the dosage of the current drug, combination or augmentation, and switch strategies, that is, introducing a new drug to replace the old one (201).

To date, the only antidepressant drug that showed evidence of efficacy in bipolar depression is fluoxetine but only when given combined with olanzapine (202,203) which allowed the FDA to approve variable fixed-dose olanzapine-fluoxetine combinations (OFCs) for the treatment of acute bipolar I depression. Among atypical antipsychotics, which may not work as a class in this specific indication (204), quetiapine monotherapy is at present the only both FDA- and EMA-approved treatment for bipolar depression. The BOLDER study group I (205) and II (206) evaluated the efficacy, safety, and tolerability of 600 and 300 mg/day of quetiapine versus placebo in the treatment of bipolar I and II depression. The results were subsequently confirmed in three more trials.

*Augmentation therapy*

Few studies are available to provide clinicians with the next best treatment to use if a mood stabilizer plus an antidepressant fails to help patients with bipolar depression. Some evidence has been obtained for adjunctive modafinil (200 mg/day), a non-addictive stimulant agent used for narcolepsy (207). Adjunctive pramipexole, a dopamine agonist, showed positive results in a preliminary placebo-controlled RCT in patients with TRD (208) when added to on-going stabilizer treatment for 6 weeks. A small open trial, randomized, on lamotrigine provided additional support for the adjunctive use of the MAOI tranylcypromine for the treatment of refractory bipolar depression (209). In a randomized, placebo-controlled, double-blind, add-on study of an N-methyl-D-aspartate antagonist in bipolar TRD, Diazgranados et al. (210) showed robust and rapid antidepressant effects resulting from a single intravenous dose of ketamine hydrochloride, a non-competitive NMDA antagonist, in subjects with lithium or valproate, but future studies should examine strategies for long-term maintenance of ketamine's rapid antidepressant response. Van der Loos et al. (211) proved the efficacy of lamotrigine as an adjunctive treatment for bipolar depressed patients taking lithium. The addition of paroxetine to non-responders did not appear to provide further benefit (212). Nierenberg et al. (213) performed the first RCT assessing the effectiveness and safety of antidepressant augmentation with lamotrigine, inositol, and risperidone in depressed bipolar I or bipolar II patients non-responsive to a combination of adequate doses of established mood stabilizers plus at least one antidepressant. Patients were enrolled in the NIMH Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). While no differences were found in primary pairwise comparison analyses of open-label augmentation with lamotrigine, inositol, or risperidone, *post-hoc* secondary analyses suggested that lamotrigine may be superior to inositol and risperidone in improving treatment-resistant bipolar depression. Nierenberg (214) proposed a case report of treatment-resistant bipolar depression with a robust remission after treatment with the combination of buspirone (5 mg) and melatonin (3 mg) plus bupropion (75 mg) added to lithium and lamotrigine (with prior failure of high-dose lithium and lamotrigine alone). The use of triiodothyronine as an augmentation agent in treatment-resistant bipolar depressed patients was studied in a retrospective chart review study by Kelly and Lieberman (215). T3 was prescribed at an average dose of 90.4 μg (range 13–188 μg). It was well tolerated and a high percentage of patients improved. Augmentation with T3 should be considered in cases of treatment-resistant bipolar depression. The use of aripiprazole in bipolar TRD was assessed in some studies. Kemp et al. (216) conducted a chart review on 12 patients with treatment-resistant bipolar disorder who received aripiprazole augmentation for the relief of an acute major depressive episode. After 8 weeks of treatment, 33% of patients demonstrated a response, but 42% of patients developed akathisia. This report, though limited by its small sample size and naturalistic design, suggests that the usefulness of aripiprazole in the treatment of bipolar depression may be limited by akathisia. Preliminary naturalistic observations on the use of adjunctive aripiprazole in bipolar TRD come from an open study on outpatients assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD), concluding that it is effective and generally well tolerated, but controlled trials are warranted (217).

For the other agents, studies have been performed on bipolar depression, but not including specifically bipolar patients with TRD. If we consider that first-line recommendations provided by the international guidelines on the treatment of bipolar depression (218–220) include the use of antidepressants with lithium or a mood stabilizer (lamotrigine, valproate) and two new antipsychotics, such as quetiapine and olanzapine-fluoxetine combination, we can consider all other options as second-line when the first-line treatment fails, but studies on patients specifically diagnosed with bipolar TRD are still lacking.

*Non-pharmacologic strategies*

In patients with refractory and severe bipolar I and bipolar II depression, the use of *electroconvulsive therapy* (ECT) should be considered, as this was shown to be one of the most effective treatments (221,222). Kessler et al. (223) conducted the first randomized controlled trial that aimed to investigate whether electroconvulsive therapy was better than pharmacological treatment in bipolar TRD.

The available data on vagus nerve stimulation (VNS) for the treatment of resistant bipolar depression showed some efficacy in reducing depressive symptoms in the short and long term mainly in open studies. On the contrary, evidences from the only double-blind study are inconclusive, suggesting that further clinical trials are needed to confirm its efficacy (224).

## Conclusions

A relatively wide variety of treatment options for unipolar TRD are available, even if their limited efficacy

is complicated by a lack of consensus on the definition of TRD itself. The use of stepwise treatment algorithms should be considered in TRD patients, regardless of whether they suffer from unipolar or bipolar depression. Antidepressant switching strategies have shown modest efficacy, and their use is not free of risks. Augmentation or combination with lithium or atypical antipsychotics (particularly aripiprazole, quetiapine, and olanzapine) appears as a valid option for both conditions, and the same occurs with ECT. Other non-pharmacological strategies such as deep brain stimulation may be promising alternatives for the future. The use of CBT is recommended for unipolar TRD, but there is no evidence supporting its use in bipolar TRD.

In spite of that, several novel therapeutic options are currently being investigated as promising alternatives, targeting the neurotransmitter system outside of the standard monoamine hypothesis. Very few studies have investigated clinical, genetic, and sociodemographic features taking into account multiple treatments failure (1,33). Studies on patients specifically selected on the basis of their TRD are needed in order to provide much etiologic information on demographic, clinical, and genetic factors associated to treatment-resistance, and to facilitate the identification of more effective treatment strategies.

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## References

1. Fava M. Diagnosis and definition of treatment-resistant depression. Biol Psychiatry. 2003;53:649–59.
2. Nemeroff CB. The burden of severe depression: a review of diagnostic challenges and treatment alternatives. J Psychiatr Res. 2007;41:189–206.
3. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am. 1996;19:179–200.
4. Crown WH, Finkelstein S, Berndt ER, Ling D, Poret AW, Rush AJ, et al. The impact of treatment-resistant depression on health care utilization and costs. J Clin Psychiatry. 2002; 63:963–71.
5. Ivanova JI, Birnbaum HG, Kidolezi Y, Subramanian G, Khan SA, Stensland MD. Direct and indirect costs of employees with treatment-resistant and non-treatment-resistant major depressive disorder. Curr Med Res Opin. 2010;26:2475–84.
6. Fostick L, Silberman A, Beckman M, Spivak B, Amital D. The economic impact of depression: resistance or severity? Eur Neuropsychopharmacol. 2010;20:671–5.
7. Keller MB. Issues in treatment-resistant depression. J Clin Psychiatry. 2005;66 Suppl 8:5–12.
8. Pacchiarotti I, Mazzarini L, Colom F, Sanchez-Moreno J, Girardi P, Kotzalidis GD, et al. Treatment-resistant bipolar depression: towards a new definition. Acta Psychiatr Scand. 2009;120:429–40.
9. Kornstein SG, Schneider RK. Clinical features of treatment-resistant depression. J Clin Psychiatry. 2001;62 Suppl 16: 18–25.
10. Mendlewicz J, Massat I, Linotte S, Kasper S, Konstantinidis A, Lecrubier Y, et al.; Group for the Study of Resistant Depression (GSRD). Identification of clinical factors associated with resistance to antidepressants in bipolar depression: results from an European Multicentre Study. Int Clin Psychopharmacol. 2010;25:297–301.
11. Fagiolini A, Kupfer DJ. Is treatment-resistant depression a unique subtype of depression? Biol Psychiatry. 2003;53: 640–8.
12. O'Reardon JP. Pharmacologic and therapeutic strategies in treatment-resistant depression. Introduction and clinical presentations. CNS Spectr. 2009;14(3 Suppl 4):4–6.
13. Serretti A, Mandelli L. The genetics of bipolar disorder: genome 'hot regions', genes, new potential candidates and future directions. Mol Psychiatry. 2008;13:742–71.
14. Howland RH, Rush AJ, Wisniewski SR, Trivedi MH, Warden D, Fava M, et al. Concurrent anxiety and substance use disorders among outpatients with major depression: clinical features and effect on treatment outcome. Drug Alcohol Depend. 2009;99:248–60.
15. Rane LJ, Fekadu A, Wooderson S, Poon L, Markopoulou K, Cleare AJ. Discrepancy between subjective and objective severity in treatment-resistant depression: prediction of treatment outcome. J Psychiatr Res. 2010;44:1082–7.

16. Amital D, Fostick L, Silberman A, Beckman M, Spivak B. Serious life events among resistant and non-resistant MDD patients. J Affect Disord. 2008;110:260–4.
17. Krishnan KR. Comorbidity and depression treatment. Biol Psychiatry. 2003;53:701–6.
18. Correa R, Akiskal H, Gilmer W, Nierenberg AA, Trivedi M, Zisook S. Is unrecognized bipolar disorder a frequent contributor to apparent treatment resistant depression? J Affect Disord. 2010;127:10–18.
19. Lee MS, Lee HY, Kang SG, Yang J, Ahn H, Rhee M, et al. Variables influencing antidepressant medication adherence for treating outpatients with depressive disorders. J Affect Disord. 2010;123:216–21.
20. Colom F, Vieta E, Martinez-Aran A, Reinares M, Benabarre A, Gasto C. Clinical factors associated with treatment noncompliance in euthymic bipolar patients. J Clin Psychiatry. 2000;61:549–55.
21. Fekadu A, Wooderson SC, Markopoulo K, Donaldson C, Papadopoulos A, Cleare AJ. What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies. J Affect Disord. 2009;116:4–11.
22. Nierenberg AA, Amsterdam JD. Treatment-resistant depression: definition and treatment approaches. J Clin Psychiatry. 1990;51 Suppl:39–47.
23. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–62.
24. Dunner DL, Rush AJ, Russell JM, Burke M, Woodard S, Wingard P, et al. Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. J Clin Psychiatry. 2006;67:688–95.
25. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006; 163:1905–17.
26. Shergill SS, Robertson MM, Stein G, Bernadt M, Katona CL. Outcome in refractory depression. J Affect Disord. 1999;54:287–94.
27. O'Leary DA, Lee AS. Seven year prognosis in depression. Mortality and readmission risk in the Nottingham ECT cohort. Br J Psychiatry. 1996;169:423–9.
28. Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. Can J Psychiatry. 2007; 52:46–54.
29. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. J Clin Psychiatry. 1997;58 Suppl 13:23–9.
30. Souery D, Amsterdam J, de Montigny C, Lecrubier Y, Montgomery S, Lipp O, et al. Treatment resistant depression: methodological overview and operational criteria. Eur Neuropsychopharmacol. 1999;9:83–91.
31. Greden JF. The burden of disease for treatment-resistant depression. J Clin Psychiatry. 2001;62 Suppl 16:26–31.
32. Souery D, Lipp O, Massat I, Mendlewicz J. The characterization and definition of treatment-resistant mood disorders. In: Amsterdam JD, Hornig M, Nierenberg AA, editors. Treatment-resistant mood disorders. New York: Cambridge University Press; 2001. p. 3–29.
33. Souery D, Oswald P, Massat I, Bailer U, Bollen J, Demyttenaere K, et al.; Group for the Study of Resistant Depression. Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. J Clin Psychiatry. 2007;68:1062–70.
34. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al.; STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006;163:28–40.
35. Martinez-Arán A, Vieta E, Chengappa KN, Gershon S, Mullen J, Paulsson B. Reporting outcomes in clinical trials for bipolar disorder: a commentary and suggestions for change. Bipolar Disord. 2008;10:566–79.
36. Sachs GS. Treatment-resistant bipolar depression. Psychiatr Clin North Am. 1996;19:215–36.
37. Yatham LN, Calabrese JR, Kusumakar V. Bipolar depression: criteria for treatment selection, definition of refractoriness, and treatment options. Bipolar Disord. 2003;5:85–97.
38. Gitlin M. Treatment-resistant bipolar disorder. Mol Psychiatry. 2006;11:227–40.
39. Weisler RH, Calabrese JR, Thase ME, Arvekvist R, Stening G, Paulsson B, et al. Efficacy of quetiapine monotherapy for the treatment of depressive episodes in bipolar I disorder: a post hoc analysis of combined results from 2 double-blind, randomized, placebo-controlled studies. J Clin Psychiatry. 2008;69:769–82.
40. Young AH, McElroy SL, Bauer M, Philips N, Chang W, Olausson B, et al.; EMBOLDEN I (Trial 001) Investigators. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). J Clin Psychiatry. 2010;71: 150–62.
41. McElroy SL, Weisler RH, Chang W, Olausson B, Paulsson B, Brecher M, et al.; EMBOLDEN II (Trial D1447C00134) Investigators. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). J Clin Psychiatry. 2010;71:163–74.
42. Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry. 2003;60:1079–88.
43. Tohen M, Case M, Trivedi MH, Thase ME, Burke SJ, Durell TM. Olanzapine/fluoxetine combination in patients with treatment-resistant depression: rapid onset of therapeutic response and its predictive value for subsequent overall response in a pooled analysis of 5 studies. J Clin Psychiatry. 2010;71:451–62.
44. Thase ME, MacFadden W, Weisler RH, Chang W, Paulsson B, Khan A, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). J Clin Psychopharmacol. 2006;26:600–9.
45. Berk M, Ng F, Wang WV, Calabrese JR, Mitchell PB, Malhi GS, et al. The empirical redefinition of the psychometric criteria for remission in bipolar disorder. J Affect Disord. 2008;106:153–8.
46. Ustün TB, Kessler RC. Global burden of depressive disorders: the issue of duration. Br J Psychiatry. 2002;181: 181–3.
47. Mueller TI, Keller MB, Leon AC, Solomon DA, Shea MT, Coryell W, et al. Recovery after 5 years of unremitting major depressive disorder. Arch Gen Psychiatry. 1996;53: 794–9.
48. Nierenberg AA, White K. What next? A review of pharmacologic strategies for treatment resistant depression. Psychopharmacol Bull. 1990;26:429–60.
49. Dunner DL, Rush AJ, Russell JM, Burke M, Woodard S, Wingard P, et al. Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. J Clin Psychiatry. 2006;67:688–95.
50. Vieta E, Nieto E, Autet A, Rosa AR, Goikolea JM, Cruz N, et al. A long-term prospective study on the outcome of

bipolar patients treated with long-acting injectable risperidone. World J Biol Psychiatry. 2008;9:219–24.
51. Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A. Residual symptoms after partial remission: an important outcome in depression. Psychol Med. 1995;25: 1171–80.
52. Kennedy N, Abbott R, Paykel ES. Longitudinal syndromal and sub-syndromal symptoms after severe depression: 10-year follow-up study. Br J Psychiatry. 2004;184:330–6.
53. Fekadu A, Wooderson SC, Markopoulou K, Cleare AJ. The Maudsley staging method for treatment-resistant depression: prediction of longer-term outcome and persistence of symptoms. J Clin Psychiatry. 2009;70:952–7.
54. Ghaemi SN, Rosenquist KJ, Ko JY, Baldassano CF, Kontos NJ, Baldessarini RJ. Antidepressant treatment in bipolar versus unipolar depression. Am J Psychiatry. 2004; 161:163–5.
55. Pacchiarotti I, Valentí M, Bonnin CM, Rosa AR, Murru A, Kotzalidis GD, et al. Factors associated with initial treatment response with antidepressants in bipolar disorder. Eur Neuropsychopharmacol. 2011;21:362–9.
56. Adli M, Berghöfer A, Linden M, Helmchen H, Müller-Oerlinghausen B, Mackert A, et al. Effectiveness and feasibility of a standardized stepwise drug treatment regimen algorithm for inpatients with depressive disorders: results of a 2-year observational algorithm study. J Clin Psychiatry. 2002;63:782–90.
57. Adli M, Bauer M, Rush AJ. Algorithms and collaborative-care systems for depression: are they effective and why? A systematic review. Biol Psychiatry. 2006;59:1029–38.
58. Adli M, Rush AJ, Möller HJ, Bauer M. Algorithms for optimizing the treatment of depression: making the right decision at the right time. Pharmacopsychiatry. 2003;36 Suppl 3:S222–9.
59. Trivedi MH, Rush AJ, Crismon ML, Kashner TM, Toprac MG, Carmody TJ, et al. Clinical results for patients with major depressive disorder in the Texas Medication Algorithm Project. Arch Gen Psychiatry. 2004;61:669–80.
60. Baldessarini RJ, Vieta E, Calabrese JR, Tohen M, Bowden CL. Bipolar depression: overview and commentary. Harv Rev Psychiatry. 2010;18:143–57.
61. Mitchell PB, Malhi GS. Bipolar depression: phenomenological overview and clinical characteristics. Bipolar Disord. 2004;6:530–9.
62. Hirschfeld RM, Williams JB, Spitzer RL, Calabrese JR, Flynn L, Keck PE Jr, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. Am J Psychiatry. 2000;157: 1873–5.
63. Kiejna A, Pawłowski T, Dudek D, Lojko D, Siwek M, Roczeń R, et al. The utility of Mood Disorder Questionnaire for the detection of bipolar diathesis in treatment-resistant depression. J Affect Disord. 2010;124:270–4.
64. Mischoulon D, Nierenberg AA, Kizilbash L, Rosenbaum JF, Fava M. Strategies for managing depression refractory to selective serotonin reuptake inhibitor treatment: a survey of clinicians. Can J Psychiatry. 2000;45:476–81.
65. Shergill SS, Katona CL. Pharmacological choices after one antidepressant fails: a survey of UK psychiatrists. J Affect Disord. 1997;43:19–25.
66. Adli M, Baethge C, Heinz A, Langlitz N, Bauer M. Is dose escalation of antidepressants a rational strategy after a medium-dose treatment has failed? A systematic review. Eur Arch Psychiatry Clin Neurosci. 2005;255:387–4.
67. Baumann P, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al.; Arbeitsge-meinschaft fur neuropsychopharmakologie und pharmakopsychiatrie. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. Pharmacopsychiatry. 2004;37:243–65.
68. Pridmore S, Turnier-Shea Y. Medication options in the treatment of treatment-resistant depression. Aust N Z J Psychiatry. 2004;38:219–25.
69. Fava M, Rush AJ. Current status of augmentation and combination treatments for major depressive disorder: a literature review and a proposal for a novel approach to improve practice. Psychother Psychosom. 2006;75:139–53.
70. Davidson J, McLeod M, Law-Yone B, Linnoila M. A comparison of electroconvulsive therapy and combined phenelzine-amitriptyline in refractory depression. Arch Gen Psychiatry. 1978;35:639–42.
71. Fava M, Rosenbaum JF, McGrath PJ, Stewart JW, Amsterdam JD, Quitkin FM. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. Am J Psychiatry. 1994; 151:1372–4.
72. Fava M, Alpert J, Nierenberg A, Lagomasino I, Sonawalla S, Tedlow J, et al. Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and nonresponders to fluoxetine. J Clin Psychopharmacol. 2002;22:379–87.
73. Perlis RH, Iosifescu DV, Alpert J, Nierenberg AA, Rosenbaum JF, Fava M. Effect of medical comorbidity on response to fluoxetine augmentation or dose increase in outpatients with treatment-resistant depression. Psychosomatics. 2004;45:224–9.
74. Nelson JC, Mazure CM, Jatlow PI, Bowers MB Jr, Price LH. Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. Biol Psychiatry. 2004;55: 296–300.
75. Joffe RT, MacQueen GM, Marriott M, Young LT. One-year outcome with antidepressant—treatment of bipolar depression. Acta Psychiatr Scand. 2005;112:105–9.
76. Maes M, Vandoolaeghe E, Desnyder R. Efficacy of treatment with trazodone in combination with pindolol or fluoxetine in major depression. J Affect Disord. 1996;41:201–10.
77. Ferreri M, Lavergne F, Berlin I, Payan C, Puech AJ. Benefits from mianserin augmentation of fluoxetine in patients with major depression non-responders to fluoxetine alone. Acta Psychiatr Scand. 2001;103:66–72.
78. Licht RW, Qvitzau S. Treatment strategies in patients with major depression not responding to first-line sertraline treatment. A randomised study of extended duration of treatment, dose increase or mianserin augmentation. Psychopharmacology (Berl). 2002;161:143–51.
79. Carpenter LL, Jocic Z, Hall JM, Rasmussen SA, Price LH. Mirtazapine augmentation in the treatment of refractory depression. J Clin Psychiatry. 1999;60:45–9.
80. Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. Biol Psychiatry. 2002;51:183–8.
81. McGrath PJ, Stewart JW, Fava M, Trivedi MH, Wisniewski SR, Nierenberg AA, et al. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. Am J Psychiatry. 2006;163:1531–41.
82. Berlanga C, Ortega-Soto HA. A 3-year follow-up of a group of treatment-resistant depressed patients with a MAOI/tricyclic combination. J Affect Disord. 1995;34: 187–92.
83. König F, Wolfersdorf M. Combination therapy using moclobemide with tricyclic and tetracyclic antidepressants to treat therapy-resistant depression. Pharmacopsychiatry. 1997;30:93–6.

84. Joffe RT, Bakish D. Combined SSRI-moclobemide treatment of psychiatric illness. J Clin Psychiatry. 1994;55:24–5.
85. Hawley CJ, Quick SJ, Ratnam S, Pattinson HA, McPhee S. Safety and tolerability of combined treatment with moclobemide and SSRIs: a systematic study of 50 patients. Int Clin Psychopharmacol. 1996;11:187–91.
86. Amsterdam JD, García-España F, Rosenzweig M Clomipramine augmentation in treatment-resistant depression. Depress Anxiety. 1997;5:84–90.
87. Lam RW, Hossie H, Solomons K, Yatham LN. Citalopram and bupropion-SR: combining versus switching in patients with treatment-resistant depression. J Clin Psychiatry. 2004;65:337–40.
88. Lucca A, Serretti A, Smeraldi E. Effect of reboxetine augmentation in SSRI resistant patients. Hum Psychopharmacol. 2000;15:143–5.
89. Harkin A, Nally R, Kelly JP, Leonard BE. Effects of reboxetine and sertraline treatments alone and in combination on the binding properties of cortical NMDA and beta1-adrenergic receptors in an animal model of depression. J Neural Transm. 2000;107:1213–27.
90. Rubio G, San L, López-Munoz F, García-García P, Alamo C. Combination therapy with reboxetine for major depression patients who are partial or nonresponders to serotonin selective reuptake inhibitors. Actas Esp Psiquiatr. 2003;31:315–24.
91. Rubio G, San L, López-Muñoz F, Alamo C. Reboxetine adjunct for partial or nonresponders to antidepressant treatment. J Affect Disord. 2004;81:67–72.
92. Papakostas GI, Shelton RC, Smith J, Fava M. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. J Clin Psychiatry. 2007;68:826–31.
93. Thase ME, Rush AJ, Howland RH, Kornstein SG, Kocsis JH, Gelenberg AJ, et al. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. Arch Gen Psychiatry. 2002;59: 233–9.
94. Fava M, Dunner DL, Greist JH, Preskorn SH, Trivedi MH, Zajecka J, et al. Efficacy and safety of mirtazapine in major depressive disorder patients after SSRI treatment failure: an open-label trial. J Clin Psychiatry. 2001;62:413–20.
95. Poirier MF, Boyer P. Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomised comparison. Br J Psychiatry. 1999;175:12–16.
96. Bschor T, Baethge C. No evidence for switching the antidepressant: systematic review and meta-analysis of RCTs of a common therapeutic strategy. Acta Psychiatr Scand. 2010; 121:174–9.
97. Bauer M, Whybrow PC, Angst J, Versiani M, Möller HJ; World Federation of Societies Biological Psychiatry Task Force on Treatment Guidelines for Unipolar Depressive Disorders. 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. 2002;3:5–43.
98. Bauer M, Whybrow PC, Angst J, Versiani M, Möller HJ; World Federation of Societies of Biological Psychiatry (WFSBF) Task Force on Treatment Guidelines for Unipolar Depressive Disorders. 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. 2002;3:69–86.
99. Stein G, Bernadt M. Lithium augmentation therapy in tricyclic-resistant depression. A controlled trial using lithium in low and normal doses. Br J Psychiatry. 1993;162: 634–40.
100. Baumann P, Nil R, Souche A, Montaldi S, Baettig D, Lambert S, et al. A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. J Clin Psychopharmacol. 1996;16:307–14.
101. Joffe RT. Treating mood disorders. J Psychiatry Neurosci. 2003;28:9–10.
102. Nierenberg AA, Papakostas GI, Petersen T, Montoya HD, Worthington JJ, Tedlow J, et al. Lithium augmentation of nortriptyline for subjects resistant to multiple antidepressants. J Clin Psychopharmacol. 2003;23:92–5.
103. Crossley NA, Bauer M. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. J Clin Psychiatry. 2007;68:935–40.
104. Fava M, Rosenbaum JF, McGrath PJ, Stewart JW, Amsterdam JD, Quitkin FM. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. Am J Psychiatry. 1994;151: 1372–4.
105. Crossley NA, Bauer M. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. J Clin Psychiatry. 2007;68:935–40.
106. Gutierrez RL, McKercher RM, Galea J, Jamison KL. Lamotrigine augmentation strategy for patients with treatment-resistant depression. CNS Spectr. 2005;10: 800–5.
107. Barbee JG, Jamhour NJ. Lamotrigine as an augmentation agent in treatment-resistant depression. J Clin Psychiatry. 2002;63:737–41.
108. Barbosa L, Berk M, Vorster M. A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes. J Clin Psychiatry. 2003;64:403–7.
109. Santos MA, Rocha FL, Hara C. Efficacy and safety of antidepressant augmentation with lamotrigine in patients with treatment-resistant depression: a randomized, placebo-controlled, double-blind study. Prim Care Companion J Clin Psychiatry. 2008;10:187–90.
110. Joffe R, Nobrega J, Kish S, Calvo R, Dixon L, Wilson J. Desipramine reduces plasma but not brain thyroxine levels. Biol Psychiatry. 1993;33:293–4.
111. Aronson R, Offman HJ, Joffe RT, Naylor CD. Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. Arch Gen Psychiatry. 1996;53:842–8.
112. Appelberg BG, Syvälahti EK, Koskinen TE, Mehtonen OP, Muhonen TT, Naukkarinen HH. Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. J Clin Psychiatry. 2001;62:448–52.
113. Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007;68:843–53.
114. Berman RM, Fava M, Thase ME, Trivedi MH, Swanink R, McQuade RD, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled

study in patients with inadequate response to antidepressants. CNS Spectr. 2009;14:197–206.
115. Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol. 2008; 28:156–65.
116. Shelton RC, Tollefson GD, Tohen M, Stahl S, Gannon KS, Jacobs TG, et al. A novel augmentation strategy for treating resistant major depression. Am J Psychiatry. 2001;158: 131–4.
117. Thase ME, Corya SA, Osuntokun O, Case M, Henley DB, Sanger TM, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. J Clin Psychiatry. 2007;68:224–36.
118. Shelton RC, Williamson DJ, Corya SA, Sanger TM, Van Campen LE, Case M, et al. Olanzapine/fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. J Clin Psychiatry. 2005;66:1289–97.
119. Corya SA, Williamson D, Sanger TM, Briggs SD, Case M, Tollefson G. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. Depress Anxiety. 2006;23:364–72.
120. Bobo WV, Shelton RC. Olanzapine and fluoxetine combination therapy for treatment-resistant depression: review of efficacy, safety, and study design issues. Neuropsychiatr Dis Treat. 2009;5:369–83.
121. Mahmoud RA, Pandina GJ, Turkoz I, Kosik-Gonzalez C, Canuso CM, Kujawa MJ, et al. Risperidone for treatment-refractory major depressive disorder: a randomized trial. Ann Intern Med. 2007;147:593–602.
122. Keitner GI, Garlow SJ, Ryan CE, Ninan PT, Solomon DA, Nemeroff CB, et al. A randomized, placebo-controlled trial of risperidone augmentation for patients with difficult-to-treat unipolar, non-psychotic major depression. J Psychiatr Res. 2009;43:205–14.
123. Reeves H, Batra S, May RS, Zhang R, Dahl DC, Li X. Efficacy of risperidone augmentation to antidepressants in the management of suicidality in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. J Clin Psychiatry. 2008;69:1228–336.
124. Rapaport MH, Gharabawi GM, Canuso CM, Mahmoud RA, Keller MB, Bossie CA, et al. Effects of risperidone augmentation in patients with treatment-resistant depression: results of open-label treatment followed by double-blind continuation. Neuropsychopharmacology. 2006;31: 2505–13.
125. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. Am J Psychiatry. 2009;166:980–91.
126. Papakostas GI, Worthington JJ 3rd, Iosifescu DV, Kinrys G, Burns AM, Fisher LB, et al. The combination of duloxetine and bupropion for treatment-resistant major depressive disorder. Depress Anxiety. 2006;23:178–81.
127. Inoue T, Tsuchiya K, Miura J, Sakakibara S, Denda K, Kasahara T, et al. Bromocriptine treatment of tricyclic and heterocyclic antidepressant-resistant depression. Biol Psychiatry. 1996;40:151–3.
128. Izumi T, Inoue T, Kitagawa N, Nishi N, Shimanaka S, Takahashi Y, et al. Open pergolide treatment of tricyclic and heterocyclic antidepressant-resistant depression. J Affect Disord. 2000;61:127–32.
129. Sporn J, Ghaemi SN, Sambur MR, Rankin MA, Recht J, Sachs GS, et al. Pramipexole augmentation in the treatment of unipolar and bipolar depression: a retrospective chart review. Ann Clin Psychiatry. 2000;12:137–40.
130. Lattanzi L, Dell'Osso L, Cassano P, Pini S, Rucci P, Houck PR, et al. Pramipexole in treatment-resistant depression: a 16-week naturalistic study. Bipolar Disord. 2002;4: 307–14.
131. Cassano P, Lattanzi L, Fava M, Navari S, Battistini G, Abelli M, et al. Ropinirole in treatment-resistant depression: a 16-week pilot study. Can J Psychiatry. 2005;50: 357–60.
132. Inoue T, Kitaichi Y, Masui T, Nakagawa S, Boku S, Tanaka T, et al. Pramipexole for stage 2 treatment-resistant major depression: An open study. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34:1446–9.
133. Patkar AA, Masand PS, Pae CU, Peindl K, Hooper-Wood C, Mannelli P, et al. A randomized, double-blind, placebo-controlled trial of augmentation with an extended release formulation of methylphenidate in outpatients with treatment-resistant depression. J Clin Psychopharmacol. 2006;26:653–6.
134. Ravindran AV, Kennedy SH, O'Donovan MC, Fallu A, Camacho F, Binder CE. Osmotic-release oral system methylphenidate augmentation of antidepressant monotherapy in major depressive disorder: results of a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry. 2008;69:87–94.
135. Michelson D, Adler LA, Amsterdam JD, Dunner DL, Nierenberg AA, Reimherr FW, et al. Addition of atomoxetine for depression incompletely responsive to sertraline: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007;68:582–7.
136. Dunlop BW, Crits-Christoph P, Evans DL, Hirschowitz J, Solvason HB, Rickels K, et al. Coadministration of modafinil and a selective serotonin reuptake inhibitor from the initiation of treatment of major depressive disorder with fatigue and sleepiness: a double-blind, placebo-controlled study. J Clin Psychopharmacol. 2007;27:614–9.
137. Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. J Clin Psychiatry. 2005;66: 85–93.
138. Pérez V, Gilaberte I, Faries D, Alvarez E, Artigas F. Randomised, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. Lancet. 1997;349:1594–7.
139. Moreno FA, Gelenberg AJ, Bachar K, Delgado PL. Pindolol augmentation of treatment-resistant depressed patients. J Clin Psychiatry. 1997;58:437–9.
140. Portella MJ, de Diego-Adeliño J, Ballesteros J, Puigdemont D, Oller S, Santos B, et al. Can we really accelerate and enhance the selective serotonin reuptake inhibitor antidepressant effect? A randomized clinical trial and a meta-analysis of pindolol in nonresistant depression. J Clin Psychiatry. 2010 Oct 19 (Epub ahead of print).
141. Perry EB, Berman RM, Sanacora G, Anand A, Lynch-Colonese K, Charney DS. Pindolol augmentation in depressed patients resistant to selective serotonin reuptake inhibitors: a double-blind, randomized, controlled trial. J Clin Psychiatry. 2004;65:238–43.
142. Pérez V, Soler J, Puigdemont D, Alvarez E, Artigas F. A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. Grup de Recerca en Trastorns Afectius. Arch Gen Psychiatry. 1999;56:375–9.

143. Goodwin GM, Emsley R, Rembry S, Rouillon F. 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. 2009;70:1128–37.
144. Lewy AJ, Bauer VK, Cutler NL, Sack RL. Melatonin treatment of winter depression: a pilot study. Psychiatry Res. 1998;77:57–61.
145. Furey ML, Drevets WC. Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. Arch Gen Psychiatry. 2006;63: 1121–9.
146. George TP, Sacco KA, Vessicchio JC, Weinberger AH, Shytle RD. Nicotinic antagonist augmentation of selective serotonin reuptake inhibitor-refractory major depressive disorder: a preliminary study. J Clin Psychopharmacol. 2008;28:340–4.
147. Sato Y, Yasui-Furukori N, Nakagami T, Saito M, Kaneko S. Augmentation of antidepressants with perospirone for treatment-resistant major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33: 416–8.
148. Zarate CA Jr, Singh JB, Quiroz JA, De Jesus G, Denicoff KK, Luckenbaugh DA, et al. A double-blind, placebo-controlled study of memantine in the treatment of major depression. Am J Psychiatry. 2006;163:153–5.
149. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006;63:856–64.
150. Preskorn SH, Baker B, Kolluri S, Menniti FS, Krams M, Landen JW. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. J Clin Psychopharmacol. 2008;28:631–7.
151. Sanacora G, Kendell SF, Levin Y, Simen AA, Fenton LR, Coric V, et al. Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms. Biol Psychiatry. 2007;61:822–5.
152. Rogóz Z, Skuza G, Daniel WA, Wójcikowski J, Dudek D, Wróbel A. Amantadine as an additive treatment in patients suffering from drug-resistant unipolar depression. Pharmacol Rep. 2007;59:778–84.
153. UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet. 2003;361:799–808.
154. Pearlman C. Electroconvulsive therapy in clinical psychopharmacology. J Clin Psychopharmacol. 2002;22:345–6.
155. Folkerts HW, Michael N, Tolle R, Schonauer K, Mucke S, Schulze-Monking H. Electroconvulsive therapy vs. paroxetine in treatment-resistant depression—a randomized study. Acta Psychiatr Scand. 1997;96:334–42.
156. Khalid N, Atkins M, Tredget J, Giles M, Champney-Smith K, Kirov G. The effectiveness of electroconvulsive therapy in treatment-resistant depression: a naturalistic study. J ECT. 2008;24:141–5.
157. Lisanby SH, Schlaepfer TE, Fisch HU, Sackeim HA. Magnetic seizure therapy of major depression. Arch Gen Psychiatry. 2001;58:303–5.
158. Kayser S, Bewernick BH, Grubert C, Hadrysiewicz BL, Axmacher N, Schlaepfer TE. Antidepressant effects, of magnetic seizure therapy and electroconvulsive therapy, in treatment-resistant depression. J Psychiatr Res. 2011;45: 569–76.
159. Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. Biol Psychiatry. 2000;47:276–86.
160. Rush AJ, Sackeim HA, Marangell LB George MS, Brannan SK, Davis SM, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. Biol Psychiatry. 2005;58:355–63.
161. Sackeim HA, Rush AJ, George MS, Marangell LB, Husain MM, Nahas Z, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. Neuropsychopharmacology. 2001;25:713–28.
162. Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry. 2005;58:347–54.
163. Henry TR, Bakay RA, Pennell PB, Epstein CM, Votaw JR. Brain blood-flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: II. Prolonged effects at high and low levels of stimulation. Epilepsia. 2004;45: 1064–70.
164. Daban C, Martinez-Aran A, Cruz N, Vieta E. Safety and efficacy of vagus nerve stimulation in treatment-resistant depression. A systematic review. J Affect Disord. 2008;110: 1–15.
165. Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. Biol Psychiatry. 2005;58:355–63.
166. Nahas Z, Marangell LB, Husain MM, Rush AJ, Sackeim HA, Lisanby SH, et al. Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. J Clin Psychiatry. 2005;66:1097–104.
167. George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK, Davis SM, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biol Psychiatry. 2005;58: 364–73.
168. Bajbouj M, Merkl A, Schlaepfer TE, Frick C, Zobel A, Maier W, et al. Two-year outcome of vagus nerve stimulation in treatment-resistant depression. J Clin Psychopharmacol. 2010;30:273–81.
169. Loo CK, Mitchell PB. A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy. J Affect Disord. 2005;88:255–67.
170. Herrmann LL, Ebmeier KP. Factors modifying the efficacy of transcranial magnetic stimulation in the treatment of depression: a review. J Clin Psychiatry. 2006;67:1870–6.
171. Daskalakis ZJ, Levinson AJ, Fitzgerald PB. Repetitive transcranial magnetic stimulation for major depressive disorder: a review. Can J Psychiatry. 2008;53:555–66.
172. George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport. 1995;6:1853–6.
173. George MS, Nahas Z, Molloy M, Speer AM, Oliver NC, Li XB, et al. A controlled trial of daily left prefrontal cortex TMS for treating depression. Biol Psychiatry. 2000;48: 962–70.
174. Padberg F, George MS. Repetitive transcranial magnetic stimulation of the prefrontal cortex in depression. Exp Neurol. 2009;219:2–13.
175. Berman RM, Narasimhan M, Sanacora G, Miano AP, Hoffman RE, Hu XS, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. Biol Psychiatry. 2000;47: 332–7.

176. Grunhaus L, Schreiber S, Dolberg OT, Polak D, Dannon PN. A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. Biol Psychiatry. 2003;53:324–31.
177. Fitzgerald PB, Huntsman S, Gunewardene R, Kulkarni J, Daskalakis ZJ. A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. Int J Neuropsychopharmacol. 2006;9:655–66.
178. McNamara B, Ray JL, Arthurs OJ, Boniface S. Transcranial magnetic stimulation for depression and other psychiatric disorders. Psychol Med. 2001;31:1141–6.
179. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. Int J Neuropsychopharmacol. 2002;5:73–103.
180. Lam RW, Chan P, Wilkins-Ho M, Yatham LN. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and metaanalysis. Can J Psychiatry. 2008;53:621–31.
181. Fitzgerald PB, Hoy K, Gunewardene R, Slack C, Ibrahim S, Bailey M, et al. A randomized trial of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in treatment-resistant major depression. Psychol Med. 2010:1–10.
182. Holtzheimer PE, McDonald WM, Mufti M, Kelley ME, Quinn S, Corso G, et al. Accelerated repetitive transcranial magnetic stimulation for treatment-resistant depression. Depress Anxiety. 2010;27:960–3.
183. Bretlau LG, Lunde M, Lindberg L, Undén M, Dissing S, Bech P. Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression: a double-blind, randomised, sham-controlled trial. Pharmacopsychiatry. 2008;41:41–7.
184. Berlim MT, McGirr A, Beaulieu MM, Turecki G. High frequency repetitive transcranial magnetic stimulation as an augmenting strategy in severe treatment-resistant major depression: A prospective 4-week naturalistic trial. J Affect Disord. 2011;130:312–7.
185. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45: 651–60.
186. Pallanti S, Bernardi S, Di Rollo A, Antonini S, Quercioli L. Unilateral low frequency versus sequential bilateral repetitive transcranial magnetic stimulation: is simpler better for treatment of resistant depression? Neuroscience. 2010;167:323–8.
187. Lakhan SE, Callaway E. Deep brain stimulation for obsessive-compulsive disorder and treatment-resistant depression: systematic review. BMC Res Notes. 2010;3: 60.
188. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45: 651–60.
189. Schlaepfer TE, Lieb K. Deep brain stimulation for treatment of refractory depression. Lancet. 2005;366:1420–2.
190. Jiménez F, Velasco F, Salín-Pascual R, Velasco M, Nicolini H, Velasco AL, et al. Neuromodulation of the inferior thalamic peduncle for major depression and obsessive compulsive disorder. Acta Neurochir Suppl. 2007; 97(Pt 2):393–8.
191. Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. Biol Psychiatry. 2008;64:461–7.
192. Malone DA Jr, Dougherty DD, Rezai AR, Carpenter LL, Friehs GM, Eskandar EN, et al. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. Biol Psychiatry. 2009;65:267–75.
193. Wang X, Chang C, Geng N, Li N, Wang J, Ma J, et al. Long-term effects of bilateral deep brain stimulation of the subthalamic nucleus on depression in patients with Parkinson's disease. Parkinsonism Relat Disord. 2009;15: 587–91.
194. Thase ME, Friedman ES, Biggs MM, Wisniewski SR, Trivedi MH, Luther JF, et al. Cognitive therapy versus medication in augmentation and switch strategies as secondstep treatments: a STAR*D report. Am J Psychiatry. 2007;164:739–52.
195. Scott J, Teasdale J, Paykel E, Johnson A, Abbott R, Hayhurst H, et al. Effects of cognitive therapy on psychological symptoms and social functioning in residual depression. Br J Psychiatry. 2000;177:440–6.
196. Matsunaga M, Okamoto Y, Suzuki S, Kinoshita A, Yoshimura S, Yoshino A, et al. Psychosocial functioning in patients with treatment-resistant depression after group cognitive behavioral therapy. BMC Psychiatry. 2010; 10:22.
197. Vieta E, Locklear J, Günther O, Ekman M, Miltenburger C, Chatterton ML, et al. Treatment options for bipolar depression: a systematic review of randomized, controlled trials. J Clin Psychopharmacol. 2010;30:579–90.
198. International consensus group on the evidence-based pharmachologic treatment of bipolar I and II depression. J Clin Psychiatry. 2008;69:1632–46.
199. Yatham LN, Kennedy SH, Schaffer A, Parikh SV, Beaulieu S, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord. 2009;11:225–55.
200. Gitlin MJ, Abulseoud O, Frye MA. Improving the design of maintenance studies for bipolar disorder. Curr Med Res Opin. 2010;26:1835–42.
201. Yatham LN, Kennedy SH, O'Donovan C, Parikh SV, MacQueen G, McIntyre RS, et al. Guidelines Group, CANMAT. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007. Bipolar Disord. 2006;8:721–39.
202. Goldberg JF. Optimizing treatment outcomes in bipolar disorder under ordinary conditions. J Clin Psychiatry. 2008;69(suppl3):11–19.
203. Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, et al. Efficacy of olanzapine and olanzapine–fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry. 2003;60:1079–88.
204. Cruz N, Sanchez-Moreno J, Torres F, Goikolea JM, Valentí M, Vieta E. Efficacy of modern antipsychotics in placebo-controlled trials in bipolar depression: a meta-analysis. Int J Neuropsychopharmacol. 2010;13:5–14.
205. Calabrese JR, Keck PE Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry. 2005;162: 1351–60.
206. Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, et al.; BOLDER II Study Group. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). J Clin Psychopharmacol. 2006;26:600–9.

207. Frye MA, Grunze H, Suppes T, McElroy SL, Keck PE Jr, Walden J, et al. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. Am J Psychiatry. 2007;164:1242–9.
208. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. Am J Psychiatry. 2004;161:564–66.
209. Nolen WA, Kupka RW, Hellemann G, Frye MA, Altshuler LL, Leverich GS, et al. Tranylcypromine vs. lamotrigine in the treatment of refractory bipolar depression: a failed but clinically useful study. Acta Psychiatr Scand. 2007;115:360–5.
210. Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry. 2010;67: 793–802.
211. Van der Loos ML, Mulder PG, Hartong EG, Blom MB, Vergouwen AC, de Keyzer HJ, et al.; LamLit Study Group. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. J Clin Psychiatry. 2009;70:223–31.
212. Van der Loos ML, Mulder P, Hartong EG, Blom MB, Vergouwen AC, van Noorden MS, et al.; LamLit Study Group. Efficacy and safety of two treatment algorithms in bipolar depression consisting of a combination of lithium, lamotrigine or placebo and paroxetine. Acta Psychiatr Scand. 2010;122:246–54.
213. Nierenberg AA, Ostacher MJ, Calabrese JR, Ketter TA, Marangell LB, Miklowitz DJ, et al. Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. Am J Psychiatry. 2006; 163:210–6.
214. Nierenberg AA. Low-dose buspirone, melatonin and low-dose bupropion added to mood stabilizers for severe treatment-resistant bipolar depression. Psychother Psychosom. 2009;78:391–3.
215. Kelly T, Lieberman DZ. The use of triiodothyronine as an augmentation agent in treatment-resistant bipolar II and bipolar disorder NOS. J Affect Disord. 2009;116:222–6.
216. Kemp DE, Dago PL, Straus JL, Fleck J, Karaffa M, Gilmer WS. Aripiprazole augmentation for treatment-resistant bipolar depression: sustained remission after 36 months. J Clin Psychopharmacol. 2007;27:304–5.
217. Ketter TA, Wang PW, Chandler RA, Culver JL, Alarcon AM. Adjunctive aripiprazole in treatment-resistant bipolar depression. Ann Clin Psychiatry. 2006;18:169–72.
218. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, et al.; WFSBP Task Force On Treatment Guidelines For Bipolar Disorders. 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. 2010;11:81–109.
219. Goodwin GM; Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for treating bipolar disorder: revised second edition—recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2009;23:346–88.
220. Yatham LN, Kennedy SH, Schaffer A, Parikh SV, Beaulieu S, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord. 2009;11:225–55.
221. Valenti M, Benabarre A, Bernardo M, García-Amador M, Amann B, Vieta E. [Electroconvulsive therapy in the treatment of bipolar depression]. Actas Esp Psiquiatr. 2007; 35:199–207.
222. Daly JJ, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, et al. ECT in bipolar and unipolar depression: differences in speed of response. Bipolar Disord. 2001;3: 95–104.
223. Kessler U, Vaaler AE, Schøyen H, Oedegaard KJ, Bergsholm P, Andreassen OA, et al. The study protocol of the Norwegian randomized controlled trial of electroconvulsive therapy in treatment resistant depression in bipolar disorder. BMC Psychiatry. 2010;10:16.
224. Daban C, Martinez-Aran A, Cruz N, Vieta E. Safety and efficacy of vagus nerve stimulation in treatment-resistant depression. A systematic review. J Affect Disord. 2008; 110:1–15.
225. Nierenberg AA. Predictors of response to antidepressants general principles and clinical implications. Psychiatr Clin North Am. 2003;26:345–52.