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Chapter 3

# The Pharmacological Frontiers in Treatment Resistant Major Depression*

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http://dx.doi.org/10.5772/53224

## 1. Introduction

Major depressive disorder (MDD) is a major burden for society, with a year-prevalence of 5% in the adult population. Usually MDD is treated with psychotherapy or serotonergic and noradrenergic antidepressants. With the first antidepressant, often a Selective Serotonin Reuptake Inhibitor (SSRI), 30-40% of patients achieve symptomatic remission. This rate increases to 67% after ≥4 trials with different classes of antidepressants (Rush et al., 2006). However, non-response (<50% improvement of symptom-severity) occurs frequently and is associated with prolonged suffering by patients and their family members, but also prolonged hospitalisations and increased suicide-rates.

## 2. Treatment resistant depression

Non-response to more classes of antidepressants is referred to as treatment resistant (or refractory) depression (TRD). TRD is not the same as chronic depression, as a properly treated patient might prove to be treatment resistant within 6 months, while patients suffering from chronic depression have often been undertreated or were non-adherent (also referred to as 'pseudo-TRD'). In addition, when TRD is considered, a re-evaluation of the patient might reveal unrecognized other axis I disorders (e.g. anxiety and substance abuse disorders), somatic diagnoses or bipolar disorder (Berlim and Turecki 2007a).

Inconsistencies in definitions of TRD impair exact estimations of the prevalence of TRD (Nemeroff 2007), but estimations range between 15-30% of patients. Also, inconsistent definitions diminish transparency in the field of clinical trials to identify the most efficacious next-step treatments, and impair reliable comparisons or meta-analyses of results from next-

* Parts of this chapter have been published previously in an adapted form in chapter 8 of "Keuzecriteria voor antidepressiva" (criteria for choosing an antidepressant), edited by Verkes R.J. & Ruhé H.G.

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step studies (Ruhé et al., 2006). Nevertheless, TRD is considered as the main cause of chronic depression with enduring hospitalizations, work-absenteeism and suicides. Therefore, TRD is responsible for the majority of direct and indirect costs of MDD (Beekman and van Marwijk, 2008).

## 2.1. Definitions of TRD

A systematic review of definitions of TRD used in clinical trials (Berlim and Turecki 2007b) identified six different definitions of TRD, ranging from non-response to one antidepressant (for ≤4 weeks ) to a failure to respond to multiple adequate (in terms of duration and dosage) trials of different classes of antidepressants and electroconvulsive therapy (ECT).

Unfortunately, none of the definitions has been properly operationalized, nor systematically investigated. For these definitions, it was most often not stated explicitly whether previous treatments were considered to determine TRD when these had been applied during the *current* or also during *any previous* episode. Furthermore, TRD-assessment was often unspecified regarding the adequacy and duration of previous antidepressant treatments, assessed retrospectively (based on patient-recall only), with occasional assessment of previous non-response by clinical global impression or validated rating scales. All definitions of TRD only focused on previous pharmacological treatment, leaving out psychological treatments like cognitive behavioural therapy (CBT) or interpersonal therapy (IPT).

In summary, Berlim et al. (2007) defined TRD as an episode of MDD which has not improved after at least two adequate trials of different classes of antidepressants, which is supported by the deteriorating chances of response after the second antidepressant observed in STAR*D (Rush et al., 2006;Ruhe et al., 2006). This definition assumes that treatment with drugs from the same class of antidepressants are less effective than successive treatments that apply a between class switch. There is very little evidence that actually supports this notion (Ruhe et al., 2006; Papakostas et al., 2008).

Berlim et al. (2007) suggested that consequent and international use of this definition would improve understanding of research findings and communication between investigators and clinicians. The European Medicines Agency (EMEA) revised their definition of TRD, stating that a "clinically relevant TRD is a current episode of depressive disorder which has not benefited from at least two adequate trials of antidepressant compounds of different mechanism of action" (Committee for medicinal product for human use (CHMP) 2009). This definition will define TRD for clinical registration studies of (new) antidepressant agents, especially to license next-step treatments. It will also exclude the inclusion of partial responders, and increase homogeneity of study-populations. Nevertheless, it should be taken into consideration that any definition of TRD is based on clinical parameters/outcomes, while it does not address underlying pathophysiology.

## 2.2. TRD as a dimensional concept; staging methods

The above definitions of TRD imply a dichotomy, which does not acknowledge the clinical impression of a more dimensional nature of TRD (Berlim and Turecki 2007a). Therefore, a

staging model for TRD appears more appropriate. Such a model should be able to classify patients according to their level of resistance to treatment for MDD, predict chances of future remission and guide clinical treatment selection. Like in oncology (Fagiolini and Kupfer 2003), in the future, psychopathological and biological markers for staging of TRD might be useful to better predict the course and prognosis of the disease. Several clinical variables might influence the development or level of TRD: duration of the episode, depression subtype, depression severity, and psychiatric and/or somatic co-morbidity (Berlim and Turecki 2007b).

We recently systematically reviewed the literature to identify staging models for TRD and compared these models regarding predictive utility (possibility to discriminate different levels of treatment response in relation to unresponsiveness to subsequent treatments) and reliability (adequacy of staging between and within raters) (Ruhe et al, 2012). Several staging methods have been developed: the the Antidepressant Treatment History Form (Sackeim, et al.,1990), the Thase and Rush Model (TRSM) (Thase and Rush, 1997), the European Staging Model (Souery et al.,1999), the Massachusetts General Hospital Staging model (Fava 2003) and the Maudsley Staging Model (MSM) (Fekadu et al., 2009a; Fekadu et al., 2009b), but to date, no staging model has been widely accepted.

With these models, an evolution from single antidepressant adequacy ratings, towards a multidimensional and more continuous scored staging model occurred over time, while also illness characteristics (severity and duration) have been introduced. The operationalization criteria for these models improved over time. The scoring of different treatment strategies (between/within class switching, augmentation/combination) changed according to the existing evidence. Over time, efforts to validate models improved as well.

The most comprehensive clinical staging/profiling model for TRD is the MSM, which was validated as measure for treatment resistance as well (Fekadu et al., 2009a; Fekadu et al., 2009b). The MSM summarizes the actual stage of TRD in a single score, varying between 3 and 15. Staging of TRD can also be presented in 3 ordinal categories: mild (scores = 3-6), moderate (scores = 7-10) and severe (scores = 11-15). The predictive utility of the MSM was tested by using prospective data (average treatment duration 26±16 weeks) from case notes (N=88) from all patients discharged from a specialized TRD-inpatient unit (Fekadu et al., 2009a). With logistic regression the MSM and its components (number of medications, duration of presenting episode, and severity of illness) were associated with failure to achieve remission (Hamilton Depression Rating Scale (21-items) ≥11) at discharge. Furthermore, variations of the MSM were examined by the introduction of additional items.

Duration, severity and treatment were independently associated with non-remission at discharge (OR: 2.27 (1.4-3.8), 2.14 (1.1-4.3) and 1.43 (1.1-2.0) respectively), as was the total MSM-score (OR 1.67 (1.3-2.2)). The MSM correctly predicted treatment resistance in 85.5% of the cases. A second study tested whether this model predicted clinical outcome after a longer follow-up (Fekadu et al., 2009b) . For this purpose, 62 patients (Fekadu et al., 2009b) were followed-up (median follow-up 29.5 months (IQR 19.0-52.5 months)). Of the patients, 21% remained depressed continuously, while 37.7% remained depressed for ≥50% of the

follow-up. Higher MSM scores were found to predict the persistence of a depressive episode throughout follow-up (OR = 2.01 (1.1-3.5), p= 0.015), and the presence of a depressive episode for ≥50% of time (OR 2.11 (1,3-3.6), p = .005). In contrast with the MSM, the TRSM also predicted future non-response, albeit worse than the MSM, but the TRSM failed to predict long-term clinical outcome.

## 3. Treatment options for treatment resistant depression

Regardless of the initial choice of antidepressant, about 30% to 50% of patients with MDD do not achieve full remission to adequately performed first-line treatment (Fava and Davidson, 1996). Several treatment strategies have been proposed for patients not responding sufficiently to monotherapy with an antidepressant. The strategies which are most commonly used are: 1) switching to a new antidepressant, either from within the same pharmacologic class or from a different class, 2) augmenting the antidepressant with other agents to enhance antidepressant efficacy, 3) combining 2 antidepressants from different classes, and 4) combining the antidepressant with depression-specific psychotherapy (Fava and Davidson, 1996). Potential benefits of switching are: this strategy is heuristically clear, because of less side effects compliance may be better than with augmentation/combination. Possible disadvantages of switching are: loss of partial response, and withdrawal symptoms (Papakostas, 2009). Potential benefits of augmentation/combination: therapeutic effect of the first drug is preserved, and augmentation may lead to a faster response. Possible disadvantages of combination/augmentation: more adverse effects, lower compliance, and the risk of possible drug interactions (Papkostas, 2009)

Currently, there is no consensus about which strategy should be favored for nonresponding patients, since until now no randomized clinical trials have been conducted to answer this question (Spijker and Nolen, 2010). Some authors argued in favor of augmentation strategies, instead of switching, because there is no need for a washout period between antidepressants and possible partial response to the antidepressant is maintained. Indeed, patients who have had some response may be reluctant to risk a loss of that improvement, and in this situation, augmentation may be beneficial. When effective, benefits of augmentation can be observed rapidly. In this chapter we will discuss three different augmentation strategies: Lithium augmentation, T3 augmentation, and The augmentation of atypical antipsychotics.

### 3.1. Switching

If a patient fails to respond to treatment with an antidepressant (usually an SSRI), an obvious strategy would be to switch to another antidepressant. A review by Ruhé et al. (2006) found 23 open studies and 8 randomized studies, often conducted in heterogeneous patient samples and with considerable variation in methodological standards. The response rates of the switch studies varied between 12 and 86%. No clear-cut advantage of switching between classes of antidepressants compared with switching within the same class emerged. Switching to venlafaxine showed a modest and clinically equivocal benefit over switching

between SSRIs with a number needed to treat = 13. This difference increased when the largest and methodologically poorest study was omitted (NNT=10). After a first SSRI, the majority of open studies reveal that switching to any of the current classes of antidepressants leads to a response rate of about 50%. However, in the randomized but unblinded STAR*D study the response rate after switching was lower; 26.8%, which may have been due to the inclusion of a higher proportion of patients with a chronic course of depression, a lower socioeconomic status and more somatic and psychiatric comorbidity (Rush et al., 2006). The level of treatment resistance was inversely correlated with outcome in the switch studies (Ruhé et al., 2006; Rush et al., 2006).

## 3.2. Combination

Combination treatment involves prescription of two different antidepressants at the same time. By combining two different antidepressants treatment may be more effective since different neurotransmitter systems can be influenced. Several studies have shown that combination treatment may be superior to antidepressant monotherapy. Blier et al. (2010) showed that three combination therapies (fluoxetine+mirtazapine, venlafaxine+mirtazapine, bupropion+mirtazapine) were all superior to fluoxetine monotherapy. In an earlier study, Blier et al. (2009) found that the combination of mirtazapine and paroxetine was more effective than mirtazapine or paroxetine as monotherapy. In the STAR*D study a combination of citalopram and bupropion showed a significant larger decrease of the Inventory of Depressive Symptoms (IDS) than a citalopram-buspiron combination, but the difference in the number of patients attaining remission was not significantly different (Gilmer et al., 2008). The co-med study (Rush et al., 2011) compared escitalopram-placebo with both an escitalopram-bupropion combination, and a venlafaxine-mirtazapine combination in a single-bind randomized study. In this study similar response and remission rates were found both after 12 weeks and 7 months of treatment for all three treatment conditions. When trying to explain why the Blier et al (2010) study found combination therapy superior to monotherapy, while the co-med study did not, Rush et al. noted that in their study only a small proportion of patients had melancholic features (20%), and the majority suffered from chronic depression. In the study by Blier et al. (2010) the majority of patients had melancholic features and lthe proportion of patients with a chronic course of depression was less. In conclusion, combining two different antidepressants may be useful, but this strategy has not been studied in specific subgroups of depressed patients, and it has not been compared with other strategies, i.e. lithium addition or non-selective MAOIs.

## 3.3. Augmentation

### *3.3.1. Lithium augmentation*

Lithium has been used to augment the efficacy of antidepressant medications for about 30 years. The first study to test the efficacy of this augmentation strategy in patients with major depression was performed by de Montigny et al. (1981). The authors observed a rapid response, within 48 hours, when lithium was added to the ongoing antidepressant treatment

of patients who had not responded to at least 3 weeks of treatment with tricyclic antidepressants (TCAs). The efficacy of the augmentation and its rapid response has led to relatively many studies concerning lithium augmentation. It has been well established in controlled trials that approximately one-half of all patients with treatment-refractory depression respond when lithium is added to their ongoing antidepressant treatment. The level of evidence for the efficacy of lithium augmentation is higher than that for other augmentation strategies (Fava and Davidson, 1996). Therefore, lithium augmentation should be considered a first-line treatment strategy in patients with major depression that does not sufficiently respond to standard antidepressant treatment. There are clues that lithium augmentation to TCAs has a higher efficacy than lithium added to modern antidepressants (Bruijn et al., 1998; Birkenhäger et al., 2004). However, lithium may also augment the therapeutic effects of SSRIs and venlafaxine. Whether lithium augmentation is effective for specific subtypes of major depression is unclear. The presence of melancholic features might be related to a higher efficacy of lithium augmentation: in the STAR*D study the efficacy of lithium addition appeared to be very low in a patient population, of which 12% fulfilled criteria for major depression with melancholic features (Nierenberg et al, 2006). In another study in depressed inpatients showing a high efficacy of lithium augmentation, 88% of the patients suffered from major depression with melancholic features (Bruijn et al., 1998). Whether or not patients with bipolar depression show a superior response to lithium augmentation is unknown.

The efficacy of lithium augmentation in depressed patients with psychotic features has been studied scarcely. In a small (n=15) open study, 60% of the patients achieved full remission during four weeks of lithium augmentation (Birkenhäger et al., 2009). Although the effect of lithium augmentation may appear during the first week of treatment, for other patients the effect becomes apparent within 2-6 weeks. The target lithium level should be at least 0.5 mmol/l, while levels of 0.6-0.8 mmol/l are recommended.In patients who respond to lithium augmentation, both lithium and the antidepressant should be continued for at least 12 months, with therapeutic plasma levels.

### *3.3.2. T3 augmentation*

The thyroid gland produces two hormones, triiodothyronine (T3) and levothyroxine (T4). T4 is the main hormone secreted by the thyroid, a large proportion of T4 is converted to T3 in peripheral tissues in order to perform its physiological function. T3 has been used in combination with antidepressants (mostly TCAs) in three different ways: A. during the first week of treatment with an antidepressant with the purpose of acceleration of the antidepressant effect; B. in combination with an antidepressant throughout the antidepressant trial, with the purpose of enhancement of the antidepressant effect; C. as additional treatment after apparent nonresponse to antidepressant monotherapy: T3 augmentation. In this chapter we will focus on C.T3 augmentation for refractory depression.

Triiodothyronine (T3) was first used in the treatment of depression in 1958. Early studies used T3 with TCAs to accelerate the response to TCAs. A meta analysis of six double-blind,

placebo-controlled studies (125 patients total) of T3 acceleration of tricyclics by Altshuler et al. (2001) was positive, as shown by d=0.58. Furthermore, a significant gender effect was observed, with women responding more robustly than men. By definition, these were short-term studies of 2 to 3 weeks, and no study investigated the option of continuing T3 once antidepressant response was achieved. Several placebo-controlled studies confirmed a more rapid effect in patients treated with both TCAs and T3 compared with TCA monotherapy.

Several open studies suggested that the augmentation of T3 to an ongoing treatment with TCAs leads to a response in a substantial proportion of patients with refractory depression. Aronson et al. (1996) performed a meta-analysis of 8 clinical trials of T3 augmentation comprising a total of 292 patients. The duration of T3 addition varied from 10 days to 6 weeks and the daily dose T3 was between 20 and 50 microgram. Patients receiving T3 were twice as likely to respond as controls, the NNT was 3. Aronson et al. (1996) concluded that T3 augmentation is an effective and safe method of increasing response in patients refractory to TCAs. However, most of the studies included in this meta-analysis had methodological flaws. When the authors restricted their analysis to 4 randomized double-blind studies, the effect of T3 augmentation was not significant any more.

Recently, a number of studies have examined the addition of triiodothyronine to selective serotonin reuptake inhibitors (SSRIs) in non-responders, but the data are more limited than with TCAs. A review by Cooper-Kazaz and Lerer (2008) found that there were insufficient data for a meta-analysis but that a positive trend was revealed when the available double- and single-blind studies were analyzed, response to T3 augmentation amounted to 40%. Papakostas et al. (2009) performed a meta-analysis which only included three double-blind, randomized, placebo-controlled studies. This analysis found response rates of 64.6% for SSRIs + T3 versus 58.5% for SSRI monotherapy, this difference was not significant.

The Sequenced treatment Alternatives to Relieve Depression (STAR*D) study compared SSRI augmentation with either lithium or T3 during 12 weeks in 142 depressed outpatients, who were refractory to treatment with citalopram and a second step (either augmentation with bupropion, buspirone or cognitive therapy or switching to a second antidepressant). This study revealed no statistical difference in efficacy between the treatments (Nierenberg et al., 2006). T3 was tolerated better and adherence was higher. However, remission rates were surprisingly low: 16% for lithium addition and 25% for T3 augmentation, respectively.

In conclusion, T3 augmentation, given at a daily dose of 25-50 microgram, is effective for patients who failed to respond to treatment with a TCA. Compared with lithium addition, the efficacy of T3 addition is established less firmly. It is unknown how long continuation treatment with T3 is necessary, following response to T3 augmentation.

### 3.4. Augmentation with atypical antipsychotics

First generation antipsychotics have been used to treat MDD, but extrapyramidal side effects and the risk of tardive dyskinesia limited the use of these agents. Since 1999 several case reports and open studies appeared, concerning the use of atypical antipsychotics as

adjunctive treatment in patients with insufficient response to treatment with an SSRI, also/especially in non-psychotic patients. Following these case series, a number of double-blind, placebo-controlled augmentation trials have been conducted. A recent meta-analysis by Nelson and Papakostas (2009) comprised sixteen double-blind studies. The following atypical antipsychotics were used in these 16 studies: quetiapine, olanzapine(both 5 studies), risperidone and aripiperazole (both 3 studies). The duration of the addition with the antipsychotics varied from 4-12 weeks, the majority of the studies investigated effects over 6-8 weeks. The meta-analysis by Nelson and Papakostas (2009) analyzes the efficacy of each of the antipsychotics separately. Olanzapine, quetiapine, riperidone and aripiperazole augmentation appeared to be superior to placebo addition. The effect of olanzapine addition was relatively small, with an Odds Ratio (OR) of 1.39. For the other antipsychotics the ORs varied between 1.63-2.00. With regard to the sixteen double-blind studies, included in this meta-analysis, it is remarkable that only a minority shows a statistically significant effect compared to placebo (six of sixteen studies). In four studies this failure to find a difference may have been caused by the fact that these studies were small. However, these figures suggest that the effect of augmentation with atypical antipsychotics is relatively small. Furthermore, Nelson and Papakostas (2009) find signs indicating publication bias. An unanswered question regarding the effect of augmentation with atypical antipsychotics: is it merely an effect on anxiety and sleep disturbance, or does this augmentation also has an effect on 'core symptoms' of MDD (depressed mood, psychomotor retardation, diurnal variation, weight loss)? Another unanswered question is whether augmentation with atypical antipsychotics is more effective than switching antidepressants.

It is unknown how long continuation treatment with both the antidepressant and the atypical antipsychotic is necessary, following response to augmentation with an antipsychotic.

## 4. Algorithms to treat major depressive disorder

### 4.1. Why using an algorithm?

Although MDD is considered to have a favourable prognosis, remission rates in controlled studies are considerably less than 50%. Insufficient response to antidepressant treatment is often caused by inadequately performed pharmacotherapy, i.e., suboptimal dosage or suboptimal duration of treatment. Since residual symptomatology carries a high risk of relapse during continuation treatment and, subsequently, a chronic course of depression, full remission should be the aim of treatment (Thase and Rush, 1997). Therefore, both inadequate treatment and actual treatment resistance constitute major problems in the management of patients with major depression. The use of a systematic treatment algorithm may decrease the variance and increase the appropriateness of antidepressant treatment and, therefore, improve outcome. Only a few studies compared the efficacy of a treatment algorithm with treatment as usual (TAU). The only prospective randomized trial (Bauer et al., 2009) found a higher remission rate in the algorithm-treated sample (54% versus 39% in the TAU sample).

## 4.2. The algorithm in the Dutch multidisciplinary guideline for MDD

The algorithm proposed in the most recent version of the Dutch multidisciplinary guideline for depression consists of five subsequent steps. Since antidepressants are effective in moderate to severe major depression, and in both primary and secondary care (psychiatric outpatients) there is no clear difference in efficacy between antidepressants, SSRIs, SNRIs, mirtazapine, bupropion and TCAs are good options as first antidepressant treatment. SSRIs are the most frequently used antidepressants in the first treatment step. If there is insufficient response after 6-10 weeks of treatment, the second step is to switch to another antidepressant. There is a slight preference for switching from an SSRI to a TCA or venlafaxine, although switching from one SSRI to another is also possible. Lithium augmentation has the strongest evidence in treatment resistant depression, but because of its potential poorer tolerability, lithium augmentation is chosen as third step. Most of the evidence for lithium augmentation concerns augmentation of a TCA. The fourth step consists of switching to a non-selective MAOI (preferentially tranylcypromine). Although the evidence for ECT is strong, ECT is sometimes not acceptable to patients, and its availability is limited. Therefore, ECT is the fifth step in this algorithm (Spijker and Nolen, 2010).

## 4.3. One algorithm?

Is it appropriate to use one algorithm for a very heterogeneous illness like major depression? Some of the treatment steps prove to be effective in one subtype of MDD whereas they appear less effective in another. Therefore we propose three different algorithms, after distinguishing three subtypes of major depression, based on the DSM-IV criteria for melancholic and psychotic features. The specific treatment steps in the algorithms are selected, when proven effective for the subtype of major depression.

## 4.4. Algorithm 1: Major depression without psychotic or melancholic features

Considerations: SSRIs, SNRIS, mirtazapine, bupropion, TCAs, interpersonal psychotherapy (IPT) and cognitive behavioural therapy (CBT) all appear to be effective. The efficacy of lithium augmentation is doubtful: lithium augmentation appeared to be ineffective in the third step of the STAR*D study (Nierenberg et al., 2006). This lack of efficacy could be explained by the fact that lithium levels were determined in only 50% of the patients and 50% of the lithium levels were low. An alternative explanation for the poor result is the very low prevalence of melancholic features in this patient sample (12%). Lithium augmentation appeared to be very effective in a study concerning depressed inpatients; of whom 88% had melancholic features. Non-selective MAOIs can be effective regardless of the presence of melancholic features. ECT has a higher efficacy in patients with melancholic depression, compared with patients without melancholic features. These considerations result in the following algorithm:

**Step 1.** SSRI or another modern antidepressant
**Step 2.** a second SSRI or another modern antidepressant

**Step 3.** a TCA
**Step 4.** a non-selective MAOI (preferentially tranylcypromine)

The addition of IPT or CBT can be considered with every step.

### 4.5. Algorithm 2: Major depression with melancholic features

Considerations: Treatment with SSRIs or other modern antidepressants (with the exception of venlafaxine) appears to be less effective than treatment with a TCA. SSRIs are less effective than TCAs or venlafaxine in depressed inpatients. This difference in efficacy may be explained by a higher compliance in inpatients, but it can also be due to a higher presence of melancholic features among inpatients compared with outpatients. Lithium augmentation to TCAs is (very) effective in patients with melancholic features. Lithium augmentation to venlafaxine has never been the subject of a double-blind study, but may possibly be effective, based on open studies. Non-selective MAO inhibitors may be effective, whereas the efficacy of ECT is high. Both CBT and IPT appear to be less effective in melancholic depression as opposed to non-melancholic depression. These considerations result in the following algorithm:

**Step 1.** a TCA or venlafaxine
**Step 2.** Lithium addition to a TCA
**Step 3.** a non-selective MAOI (preferentially tranylcypromine)
**Step 4.** ECT

Depending on the patient's condition, step 3 and 4 can be switched.

### 4.6. Algorithm 3: Major depression with psychotic features

Considerations: Monotherapy with a TCA is not effective according to studies from the US, while European studies found TCAs as monotherapy to be effective for psychotic depression. Whether a combination of a TCA and an antipsychotic is superior to TCA monotherapy is unclear. A Combination of venlafaxine and quetiapine proved to be superior to venlafaxine monotherapy. Treatment with lithium addition has been studied scarcely in psychotic depression, but possibly it may be effective. The efficacy of non-selective MAOIs in psychotic depression is unknown. Treatment with ECT is very effective. These consideration results in the following algorithm:

**Step 1.** TCA with/without an antipsychotic OR venlafaxine + quetiapine
**Step 2.** If Step 1 was TCA, add an antipsychotic. If Step 1 was venlafaxine switch to a TCA
**Step 3.** Lithium addition to a TCA
**Step 4.** ECT

ECT may be performed prior to step 4, especially for patients in a critical condition.

## 5. Conclusion

Treatment-resistant depression is a major health issue, since major depression is a prevalent disorder and remission is not easily attained. Futhermore, treatment-resistance appears to

be difficult to define. In this chapter, we discuss several staging methods for treatment-resistant depression. With regard to treatment options for patients who fail to respond to the first antidepressant, these consist of switching antidepressants, combining antidepressants, and augmentation strategies. Optimisation of antidepressant treatment can be achieved by applying those treatment strategies as an algorithm. In the Dutch multidisciplinary guideline for depression one standard algorithm is proposed, without considering the (limited) evidence that various subtypes of major depression respond differently to specific treatment steps. Therefore, we propose three algorithms, which are based on the limited evidence regarding the efficacy of several treatment steps for a specific subtype of major depression.

## 6. Summary

In the first part of the chapter various definitions of treatment resistant (refractory) depression (TRD) are reviewed. We conclude that there is no consensus regarding the operational criteria for TRD. For TRD, five different staging models have been developed to determine a staging level of refractoriness: the Antidepressant Treatment History Form, the Thase and Rush Staging model, the Massachusetts General Hospital Staging Model, the European Staging Model and the Maudsley Staging Model. The utility of these models will be discussed.

The second part of the chapter focuses on treatment options for TRD. Apart from switching the antidepressant, various augmentation strategies are currently applied for refractory depression, e.g. lithium addition, triiodothyronine addition and the addition of second generation antipsychotics. The advantages of these strategies will be discussed.

Finally, we will discuss the use of treatment algorithms. The algorithm for the pharmacological treatment of major depression of the Dutch multidisciplinary guidelines for depression is presented. The five subsequent steps of this algorithm (treatment with an antidepressant, switching to another antidepressant, lithium addition, switching to an MAO inhibitor, electroconvulsive therapy) will be discussed and a proposal for three different algorithms will be presented, depending on the presence or absence of melancholic and psychotic features will be discussed, as well as alternative strategies for the pharmacological treatment of TRD, which are not (yet) included in the algorithms.

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