An Overview of The Definition and Management of Treatment-Resistant Depression

Diane Bird BSc, MSc[1], Peter M. Haddad MBChB, MRCPsych, M.D.[2]
Serdar M. Dursun M.D., Ph.D, FRCPC[2]

ABSTRACT:
AN OVERVIEW OF THE DEFINITION AND MANAGEMENT OF TREATMENT-RESISTANT DEPRESSION

In this article, we review the literature defining treatment-resistant depression and pharmacological strategies to manage these difficult and challenging clinical cases. Augmentation strategies reviewed in this paper are limited and include the classic and very well-established antidepressant-augmenters such as lithium and thyroid, in addition to the newer use of pindolol and tryptophan. We also present possible clinical variables which may be complicating the choice, administration and monitoring safely and effectively during switching and augmenting antidepressant drugs.

Key Words: treatment-resistant depression, depression, pharmacotherapy, psychopharmacology, lithium, thyroid hormones, pindolol, tryptophan, serotonin, ECT

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INTRODUCTION

The main goal in the treatment of patients with major depressive disorder is to relieve symptoms and thus help restore psychological wellness and functioning. Pharmacotherapy and psychotherapy are the two main cornerstones of treatment for this illness. This review is restricted to pharmacotherapy but in practice pharmacological treatment should always be combined with psychological and social interventions. Recent reviews suggest 65 to 75% of patients treated with antidepressants will have clinically significant improvement (1-8). Unfortunately, not all individuals diagnosed with depression will respond to pharmacotherapy, with 10-20% of patients not able to tolerate an antidepressant medication. Even more concerning, in patients who complete an adequate trial of antidepressant medication, 25-30% are unresponsive and have no significant decrease in symptoms (2-9). This paper reviews the literature defining treatment resistant depression (TRD) and pharmacologic strategies to manage these difficult clinical cases.

Definitions of TRD

A significant amount of variance appears in the literature when defining TRD. In a simplistic view, TRD is defined as an episode of major depression that does not respond to an adequate trial of medication and thereby does not provide the patient with adequate relief of symptoms. Yet this simplistic view is unclear and ambiguities arise in how adequate treatment and adequate relief are defined (10). Beyond these challenges there are other factors that can contribute to a patient not responding which need to be clearly ruled out before a patient's depressive episode is a "true" TRD (2-9).

Adequate Response to Treatment

When defining a poor - or non-response to treatment in clinical trials of Major Depressive Disorder (MDD), the most common measure is a lack of prespecified reduction in a depression rating scale, i.e. a less than 50% reduction in Hamilton Depression Score (HAM-D)(11). This measure is problematic since different versions of the HAM-D scale are utilized (17-, 21-, 25-item versions) causing results to be different between trials, and dependent on a different absolute number of symptoms. More concerning is that patients with considerable residual morbidity could be defined as responsive yet still have significant symptomatology. This would be true if they had a very high initial HAM-D score. To try to solve

[1]Departments of Psychiatry and Pharmacology, Dalhouise University, Halifax, NS, Canada
[2]Neuroscience and Psychiatry Unit, School of Psychiatry and Behavioural Sciences, The University of Manchester, Oxford Road, Manchester M13 9PT, UK

Yazışma Adresi / Address reprint requests to: Serdar Dursun M.D., Ph.D., FRCPC, Senior Lecturer in Psychiatry and Honorary Consultant Psychiatrist Neuroscience and Psychiatry Unit, School of Psychiatry and Behavioural Sciences, The University of Manchester, Oxford Road, Manchester M13 9PT, UK

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some of these shortcomings, alternative and more restrictive criteria for measuring non-response in clinical trials have included pre-specified absolute score of a depression rating scale (a score of over 9 on the Beck Depression Inventory Scale) or a combination of scales including a pre-specified reduction and absolute value for both scales measuring both global functioning and depressive symptoms (1,3-8).

Adequate Treatment Trial

If a patient is not responding to a treatment, physicians must first ensure that the patient has been given a high enough dose of medication for a sufficient amount of time. In the university setting, a high proportion of cases have been referred for treatment of 'TRD" that have not had a single adequate antidepressant trial (12,13). Due to the high numbers of patients not receiving an adequate trial of medication, in 1985 the World Psychiatric Association categorized treatment resistance as either absolute or relative. They define absolute therapy resistance as no response to adequate treatment with a tricyclic antidepressant (TCA) (150mg imipramine or equivalent dose for 4-6 weeks) and relative therapy resistance as no response to a non-adequate treatment regimen (14). In 1995, the definitions of absolute and relative treatment resistance were modified to reflect the knowledge that higher dosages and longer treatment periods may be necessary for response (10). The concept of relative treatment resistance is now referred to as patients who have received at least an average dose of a specific class of antidepressant for a minimally adequate time period; whereas absolute resistance refers to a patient failing to respond to a maximum non-toxic dose of a given antidepressant, with confirmed compliance over an extended treatment period (1). The similarity over time between these definitions is what is most important, namely the importance of discriminating between "true" resistance and "apparent" resistance. True resistance (i.e. the main point of definitions of absolute resistance) is due to pharmacodynamic reasons (ie. lack of sensitivity of a MS receptor to a compound). In contrast, apparent resistance (main point of relative resistance) is due to pharmacological factors including inadequate drug dosage or duration, or possibly other pharmacokinetic factors that lead to inadequate tissue levels of the drug (3-8,15). There may be also unknown factors complicating the treatment outcome, for example cholesterol levels have been linked to some symptoms of depression (for review see 16,17). Furthermore, there is also a possibility that natural ageing process may also effect the outcome (18,19).

Adequate Dosage

Underdosage of antidepressant medication has historically been known to be one of the largest causes of nonresponse to treatment. In the 1970s, reports suggested that 5 to 25% of all referrals to an outpatient clinic had been treated by general practitioner with an antidepressant at sub-therapeutic dosage (20,21). Even with this empirical evidence, in the 1980s the literature suggested that up to two-thirds of depressed patients who were judged to be refractory to antidepressants had received an inadequate dosage of TCAs (12,13,22). For the TCAs, aggressive dosing (imipramine, desipramine, trimipramine, amitriptyline and doxepin at 250rng to 300 mglday; nortripyline with plasma levels between 50mglmL to 150mg/mL) has been demonstrated to be more effective that lower dosages for many patients (22,23). It has also been approximated that 5 to 10% of patients will have subtherapeutic TCA plasma levels despite compliance with conventionally maximum dosages (e.g. 300mg/day of imipramine or 20Omg/day nortryptiline) (24). One possible reason for this inconsistency in dosage could be due to the inter-individual variability in drug metabolism, with some individuals having an enhanced capacity for metabolizing drugs making them unable to achieve therapeutic drug levels (25). Therefore, the American Psychiatric Association (1985) has recommended that plasma drug concentrations be measured as a possible aid to ensuring compliance and effective therapeutic range for drugs like imipramine, desipramine or nortryptiline that have recommended therapeutic plasma ranges.

For the Serotonin Reuptake Inhibitors (SSRIs) there is no clearly established therapeutic window. Several studies have suggested that there may be a nearly flat dose- response curve, yet a linear dose-side effect curve for most SSRIs (26-30). This may suggest that increasing the dosage may not increase the probability of response, but this is likely to increase both the side-effects and costs of the medications (31). However, when comparing raising the dose of fluoxetine to the combining of fluoxetine with either desipramine or lithium, a double-blinded trial by Fava et al (32) showed the most successful treatment for TRD was high dose fluoxetine (40-60mg/day). These results demonstrate the need to clarify what dosages of SSRI should be prescribed for greatest efficacy. Specifically, there is a need for future research on the efficacy of higher dosages of SSRIs and dose-response relationships for the relatively newer antidepressants (4-8).

Adequate Trial Length

To have an adequate trial of antidepressant medication, the trial must have a long enough duration to allow for symptom reduction. Longer medication trials allows for the natural history of the episode to remit, and therefore help distinguish between true responders and more transient placebo

responders (13). Most TCAs and SSRIs have a half-life of 20 to 58 hours, which results in steady-state plasma concentrations being achieved on average in 5 to 12 days after any given dose is commenced (33). The exception to this is the SSRI fluoxetine, which has a half-life of 24 - 330 hours for the parent drug and active metabolite respectively (33), which may account for the continued evolution of treatment response for at least 8 weeks of treatment (28). However, overall for most antidepressant, treatment beyond 6 weeks is not usually supported in reviews of the current literature (1,3-8)

Other Factors Complicating Response

If an adequate treatment response is not achieved with an adequate trial of medication before a "true" drug resistance can be envisaged, incorrect diagnosis, possible noncompliance, as well as a variety of pharmacological factors could suppress response rates and should be addressed before any alternative therapies are indicated.

Nonresponse to antidepressants can sometimes be attributed to misdiagnosis, including a unrecognized underlying medical illness (e.g. hypothyroidism, organic brain changes such as minor infarcts), which can occur in up to 46% of psychiatric inpatients (34). Similarly, concurrent psychiatric conditions such as bipolar disorder (35), panic disorder (36), premorbid personality disorder (37,38), alcoholism or drug abuse (39) can cause pseudoresistance.

Patient non-compliance with medication is often covert and as a result it is a common cause of apparent treatment resistance (40-42). Many reasons for patient non-compliance have been suggested including a breakdown in patient-doctor relationship, inadequate psychoeducation, and intolerable side effects. It is important that patients are routinely asked about their compliance with medication. A number of simple strategies can be employed to help improve compliance (43).

Other pharmacological and medical factors that could interfere with efficacy of antidepressants include concurrent prescription drugs which enhance antidepressant metabolism and so reduce antidepressant plasma levels (for review see e.g. 33,44-46).

Management of "True" Treatment Resistant Depression

After nonresponse to an initial adequate trial of an antidepressant that can not be accounted for by the other factors listed above, the likelihood of a placebo responsiveness or spontaneous remission dissipates (2-8). Often these patients are referred to as having "true" TRD. The other group of patients that represent "true" TRD include patients who have a medication intolerance and are unable to achieve or maintain an adequate therapeutic dose of an antidepressant drug due to idiosyncratic reactions or side effects. For these two groups, a wealth of treatment options exist including switching to a variety of alternative monotherapy agents or classic augmentation strategies utilizing thyroid hormone or lithium. Less commonly, patients can also be treated with a combination therapy of antidepressants or newer antidepressants (TCA or SSRI) combinations with pindolol or tryptophan. For the most challenging cases, treatment can also include the use of electroconvulsive therapy, or after the use of these extensive treatments, a serotoninergic medication cocktails (5-8).

Stages of Treatment Resistance

The utilization of a treatment algorithm has been suggested for the management of TRD, borrowing concepts from illness staging that were first described in the area of oncology (2,3,16). Thase and Rush (2) have recently suggested possible staging for TRD (Table 1) which follows the basic concept that the more resistant to treatment a patient's illness is, the further treatment should proceed. However, like all treatment algorithms that have been suggested for treatment resistant depression, this algorithm has not been validated by empirical evidence.

Tablo 1. A Simple System for Staging Antidepressant Resistance (2)

Stage	Definition
I	Failure of at least one adequate trial of one major class of antidepressant (usually an SSRI)
II	Stage I resistance plus failure of an adequate trial of an antidepressant trial in a distinctly different class from that used in stage I (usually another SSRI)
III	Stage II resistance plus failure of an adequate trial of a TCA
IV	Stage III resistance plus failure of an adequate trial of an MAO]
V	a IV resistance plus failure of a course of ECT

Switching Antidepressant Medication

For initial nonresponse to an antidepressant there are conceptual advantages associated with trying another monotherapy instead of advancing to an augmentation strategy. These advantages include lower risk for drug-drug interactions, usually less drug expense, estimated potencies of neurotransmitter uptake blockade, dose-limiting side effects, as well as following the dictum in medicine that a combination of two drugs should not be used if one drug will suffice (1-8). Depending on the initial treatment strategy employed, switching treatment could be between TCAs, between SSRIs or could be a switch between TCAs, SSRIs and MAOIs.

If the initial treatment with a TCA produces an inadequate response, it is suggested by some to switch

the TCA (such as a tertiary amine, i.e. imipramine) with another TCA (such as secondary amine, i.e. nortryptiline) (47). However, the empirical evidence for this strategy is limited and in two controlled trials examining the efficacy of this strategy, response rates under 30% were reported (48,49). In comparison, high response rates are able to be achieved when switching from a TCA to a second generation heterocyclic (such as trazodone or bupropion) (50). Intuitively, it makes more sense that this switch would be beneficial since these drugs differ in both chemical structure and side-effect profiles. In a limited number of studies of TRD, bupropion has been reported to cause significant change in global functioning and decrease in symptoms compared to placebo, and trazodone has been reported to have a response rate of around 56% (50-52). In contrast to both of these methods, higher rates of response are reported for a switch from a TCA to a SSRI. Switching from a TCA to a SSRI has been supported in many smaller double blind trials, reporting an average response rate of 50% (1). Recently, 90% of imipramine (TCA) nonresponders completed a treatment trial with sertraline with an average response rate of 65% (24).

Many patients treated for depression receive an SSRIs as a first-line agent. Therefore many patients treated for true TRD have been resistant to one adequate trial of an SSRI and are being switched to either a) another SSRI; b) a TCA; c) a Reversible MAOI (RMA0 such as moclobemide); or d) one of the newer antidepressant agents (3). These newer agents include the Selective Dopamine-Reuptake Inhibitors (SSDI, such as bupropion), the Selective Serotonin Norepinephrine Reuptake Inhibitors (SNRI, such as venlafaxine) and the Serotonin Reuptake Inhibitor/Receptor Blockers (such as nefazadone), There is a large amount of evidence in open-labelled studies to suggest that the use of a second SSRI after nonresponse to one will be beneficial in between 42 to 71 % of cases (2,53-55). However, no controlled double-blinded trials have addressed this question, and thus the current need for research in this area.

The possibility of using a TCA as a second-line agent after SSRI nonresponse has demonstrated some benefit with 43% of patients responding when switched to imipramine and up to 61 % of patients responding after being switched to a noradrenergic TCA (24,56). Currently, there is a lack of extensive data to support the use of TCAs for treatment of SSRI nonresponders, and similarly the new alternative agents such as bupropion, venlafaxine and nefazodone have not been studied in controlled trials (2). However, these newer agents are different enough from SSRIs that theoretically they may be beneficial, especially since compared to TCAs they are safer in overdose than TCA. Often a second line agent may be chosen because of the specific symptoms of the patient. For example, some evidence exists to favour venlafaxine for severe cases (57), bupropion for patients with sexual dysfunction (a common side effect of SSRIs, TCAs and MA0Is) (58) and nefazodone for patients with insomnia (59). Furthermore, if atypical features are present after a nonresponse to a first-line SSRI agent or if panic attacks are present, a MAOI or RIMA should be considered after a suitable washout period.

One important clinical point to consider during antidepressant switching is the occurence of antidepressant discontinuation (or withdrawal) syndromes which may complicate the management of depression during the switching-period. It is criticak for the treating-clinician to keep in mind the possibility of an antidepressant-discontinuation reaction which may mimic and may be considered as a relapse of the disorder (60-62). Discontinuation syndromes are recognised with all the major antidepressant classes as well as various miscellaneous antidepressants (60,62). There is a danger that discontinuation symptoms from the antidepressant that is being stopped may be mistaken for side effects of the new antidepressant that is being started leading to inappropriate management (61). The likelihood of this occurring is increased as many clinicians lack awareness of discontinuation phenomenon (63,64). Occasionally discontinuation symptoms can be very severe and cause significant disability (65). The potential benefits of tapering the first antidepressant, in an attempt to minimise discontinuation symptoms, must be balanced against the risks of delaying starting the new antidepressant. Tapering is usually not required when switching between antidepressants of the same class as discontinuation symptoms are fairly uncommon in this situation (62) though there are exceptions.

Classic Augmentation Strategies for Antidepressant -Resistant Depression

There is no widely-established consensus about the number of failed trials of a monotherapy agent that should be completed before an augmentation strategy is utilized. Recently, Thase & Rush (2) have suggested a stronger case for augmentation strategies can be made after a patient has failed a response to a SSRI and at least one other class of a newer antidepressants or TCA. However, the possible benefit that could be gained from trying antidepressants of different classes after monotherapy must be weighted against the risks of at least transient worsening of the patients symptoms. From the era of TCA, there is extensive literature on lithium and thyroid augmentation, however these strategies are not as well documented in literature involving SSRI nonresponders.

Lithium

Lithium is an antidepressant and mood stabilizer

when used alone and when used in addition to a TCA it is proposed to augment treatment by an acute synergistic effect and more slowly emerging primary antidepressant effect (24,66). The use of lithium salts in dosages of 600 to 1200 mg/day (blood levels of 0.6 to 1.0 mmol/L) has been reviewed extensively (1,67-69). Published studies that permit dose adjustments and at least 4 weeks of treatment suggest augmentation response rates in the range of 50% to 65%. In comparison to the multiple number of case reports and open studies, the five placebo controlled trials involving lithium augmentation of TCAs suggest a significantly higher response rate with lithium, with response rates as high as 80% (70-74). In contrast, there is a scare amount of contradictory evidence for the use of lithium augmentation of a SSRI. Delgado et al (75), found a 50% response to lithium augmentation of fluoxetine nonresponders and Fontaine et al (76) reported no difference in lithium augmentation of fluoxetine or desipramine. However, lithium augmentation of fluoxetine has been associated with a significantly higher number of side effects and greater number of transient responses when compared to TCA lithium augmentation (76). With the rise in the number of patients who are receiving a SSRI as a first-line treatment agent, the need for trials to fully evaluate the efficacy of lithium augmentation for SSRI non-responder is imperative, especially since the proposed mechanism of lithium augmentation (enhanced serotonergic neurotransmission) may be less relevant for patients who have already failed to benefit from a potent SSRI. However, despite its limitations in clinical practice, tolerability/side-effect profile, blood monitoring, it remains as the "gold standard antidepressant-augmenter" (5-8,77).

Thyroid Hormones

Historically, the oldest treatment strategies for TCA nonresponse was the addition of thyroid hormone. The suggested mechanisms of action include potentiation of effects on noradrenergic receptor sensitivity, increased efficiency of noradrenergic neurotransmission, and correction of subtle thyroid abnormalities (78,79). Augmentation of L-triiodothyronine (T3) is preferred over thyroxine (T4) for both theoretical and clinical grounds (80). Reviews of the literature suggest that there is variability in the outcomes of studies validating the use of T3, with approximately 25% of TRD cases responding to the addition of a TCA with 25 to 50 ug/ml/day of T3 (1). These studies, are however, often limited by the lack of parallel control groups and blinded designs (1). In the one randomized placebo-controlled trial contrasting T3 with lithium augmentation, Joffe et al (70) reported thyroid and lithium augmentation to be comparable yet significantly better than placebo augmentation. Similar to the amount of literature on the use of lithium and SSRIs, there is no literature that has validated the use of T3 augmentation for the SSRIs or newer antidepressants, and hence, it is not clear whether these treatment methods may be effective for TRD.

Combination Antidepressants

The option to combine a TCA with a SSRI has been examined in open labelled trials and been suggested to offer a potential "one-two punch" on the noradrenergic and serotonergic neurotransmission (2-8). Three open labelled studies of SSRI and TCA combinations yielded rates of response in the 25% to 65% range (32,81-83). However, routine serum levels of TCA is required with this cotherapy since all SSRIs will inhibit the cytochrome P450 system and thus raise TCA blood levels. This increase in the TCA plasma level have been associated with cardiovascular effects and possible overdose complications (1). Thus, hopefully future controlled research will be conducted to ensure that this cotherapy has a greater benefit to risk ratio for TRD patients.

The other possible combination that is recognized involves the older combination of a MAOI with a TCA (definitely not a SSRI) or the novel use of the safer RMAOI, moclobemide, with a SSRI. Several uncontrolled trials in patients with TRD have reported good results with a TCA and MAOI combination (84,85). For example, a retrospective chart review by Gander et al (86) noted that in 157 TRD patients, there was a 62% response rate after a combination of TCA-MAOI. However, the reverse use of a TCA after a failed MAOI trial is not safe and is clearly contraindicated (87). In contrast to the contraindicated combination of a SSRI with the class MAOI because of the life-threatening serotonin syndrome (88-92), the combination of an SSRI with an RMAIO is indicated to be safe. For example, one retrospective study that examined the combination of moclobemide with a low to moderate dose of an SSRI in TRD patients found an overall efficacy of 71 % with few reported side effects (93).

New Augmentation Strategies Including Pindolol and Tryptophan

Pindolol

Recently, the addition of pindolol, a presynaptic 5-HT1A and alpha- adrenergic antagonist, to ongoing antidepressant treatment has been reported to exert a rapid therapeutic response and to be effective in treating SSRI TRD patients (7-8,93-95). It is postulated that the addition of pindolol increases efficacy in treatment-resistant patients by allowing a normalization of the firing activity of the 5-HT

neurons in patients not responding to SSRIs, presumably because their 5-HT1A autoreceptors have failed to desensitize (96). The effectiveness of pindolol augmentation strategies has been examined with antidepressant medications and some, but not all, SSRIs and TCAs have demonstrated significant improvement in efficacy with this combination. Phenelizine, paroxetine, imipramine and buspirone, when combined with pindolol in open trials, have been reported to produce a rapid and dramatic improvement in the treatment of MDD symptomatology (94-99). In comparison, in open trails of sertraline combined with pindolol, no robust antidepressant effects were reported (98,94) and in two recent double-blind trails comparing fuoxetine combined with either placebo or pindolol, results are conflicting (100,101) lack of faster onset when pindolol is combined with some SSRIs is likely due to the P450 interaction (102).

The possibility of the phenylpiperazine antidepressant nefazodone producing therapeutic effects for drug-resistant patients with augmentation strategies utilizing pindolol is reported in one open-label study (93). In this trial, nefazodone and pindolol treatment in 20 MDD outpatients was well tolerated and a majority of the patients demonstrated a 50% reduction of HAM-D scores after one week of treatment. These findings suggest that nefazodone may have pharmacodynamic properties that would make it a beneficial augmentation agent.

Tryptophan

The precursor role of tryptophan in the synthesis of serotonin is well established and studies suggest that tryptophan may be an effective augmentation agent in some treatment regiments for depression (103). The use of tryptophan was first identified in case reports in the 1960s for TRD in augmentation with MA0Is (104). When combined with a TCA, tryptophan augmentation may be indicated for amitriptyline, clompramine, or for patients with insomnia, but has failed to demonstrate positive effects for all TCAs (105-107). When used with an SSRI, tryptophan has been suggested to be started at a dose of 500mg to reduce the risk of serotonin-related side effects and should be gradually increased up to 2g to 6g per day (103).

There is recent evidence that combination of tryptophan plus pindolol with nefazodone may be effective in a group of patients with TRD (8). However, further controlled trials are required to confirm the efficacy of such combination treatments.

Electroconvulsive Therapy (ECT) for TRD

After an augmentation has been unable to produce the necessary responsd, the use of ECT has been suggested in many reviews of the literature as the treatment of choice (1,2,42,108-110). Although response rates in TRD are significantly lower than response rates for less complicated cases, high response rate of 60 to 70% are reported for TRD cases (111). Although it is an effective treatment for TRD, recent literature suggests that relapse rates (around 40%) may be significantly higher for patients after ECT despite prophylactic treatment (109). It has been suggested in reviews that either high-energy unilateral or bilateral modes of treatment administration are preferred and failure should not be indicated until 12 treatments (including 8 bilateral courses) have been provided (108,109).

Treatment After Nonresponse to ECT

Patients who have failed to respond to ECT clearly represent some of the most challenging cases of TRD. Thankfully, the number of patients who will reach this stage of nonresponse may be as low as 7% (2). There is some suggestions that after a unsuccessful treatment course of ECT, there may be changes in receptor sensitivity and some patient (case report of 2 patients) may be more responsive to antidepressants (112). In case series reports, other possibilities for treatment involve the use of specific 5-HT drug cocktails, that are often not validated and possess considerable risk to patients. The combination of pheneizine, trypotophan and lithium appears to be effective in 60% of subjects with chronic TRD (113). Similarly, the use of the "New Castle Cocktail" of clomopramine, lithium and tryptophan has been effective in depressions resistant to TCA (106). Recently, five cases of highly drug-resistant MDD patients treated with the "Dalhousie Serotonin Cocktail" of pindolol, tryptophan, and nefazodone have also showed promising results (8). Although these findings are very preliminary, they do illustrate that there is still hope that pharmacotherapy may be able to provide relief following ECT failure.

Conclusions

Treatment resistant depression is a relative term, with a majority of patients who are labeled as treatment-resistant being more likely partial responders to an inappropriate trial of antidepressant medication. If an adequate medication trial has been completed, other factors must be considered before a patients is labeled TRD, including the possibility of incorrect diagnosis, poor compliance, or possible pharmacological factors that are changing the drug is ability to provide relief. In patients that are "absolute" TRD patients, we are very fortunate in the 1990s to have a wide variety of pharmacological and psychological mechanisms to try to alleviate patient

symptomatology. The pharmacological possibilities that are reviewed in this paper include switching to another antidepressant, combining antidepressants or starting a possible trial of an augmentation strategies.

Augmentation strategies reviewed in this paper are limited and include the classic use of lithium and thyroid, in addition to the newer use of pindolol and tryptophan. However, a variety of other less common and less conventional treatment strategies that are not reviewed in this paper, include augmenting with antipsychotics, buspirone, reserpine, estrogen, monoamine agonists, monoamine antagonists, and monoamine precursors (for review see 1,5). Furthermore, there is very weak evidence for the use of psychostimulant treatment, sleep deprivation and light therapy in TRD treatment.

If there is an inadequate response to augmentation, then the use of ECT has been indicated. For approximately 7% of patients who are still treatment resistant, pharmacological possibilities exist. These include the possibility of another trial of antidepressant or one of the "newer serotonin medication cocktails". However, for all of these augmentation strategies the use of drug combinations for TRD must rely on clinical or empirical rationale, where the risk/benefit ratio is very carefully considered and should be carried out in tertiary specialist psychopharmacology clinics.

For all of these possible strategies for TRD, a large amount of the literature is case reports, case series, retrospective reviews and open label trials. A review of the publications produced between 1959 and 1994 demonstrates that less than 1% of the literature is controlled studies due to both pragmatic and ethical reason (1). To overcome these difficulties, physicians must work in collaboration to create the database of patients needed to solve some of the dilemmas that plague these studies' design. Future studies must be carefully planned to include either a standard comparator group or comparison between methods currently being employed, to avoid the human and economical cost of incorrect treatment of TRD due to the lack of empirical evidence. Furthermore, the best method of approach to treatment of TRD must be identified and validated in the form of systematic algorithms to avoid confusion and "therapeutic nihilism" for both the physician and the patient.

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