REVIEW ARTICLE

Treatment Resistant Depression

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ABSTRACT
Most of the literature on Treatment Resistant Depression (TRD) has based its definition of resistance on the failure to respond to antidepressant drug treatment of adequate dose and duration. The prevalence of TRD is lowest in primary care settings and progressively increases in outpatient psychiatry settings, inpatient psychiatric settings, and academic/tertiary care settings. Strategies available for the treatment of TRD include optimization, substitution or switching, combination, and augmentation therapies. Currently there are no clear guidelines on when to substitute, combine, or augment therapies in the treatment of patients with TRD. Some new and novel therapies that show promise for the future include addition of an atypical antipsychotic to the initial antidepressant; newer pharmacologic interventions; and non-pharmacologic therapies such as vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation (DBS). The newer models of interpersonal, cognitive, and behavioral therapies offer structured, pragmatic methods to work with such difficult patients. Guidelines for psychotherapeutic intervention for TRD suggested that the therapy should be collaborative and centered on the goal of teaching new skills to improve coping with a chronic illness. A better understanding of the many facets of the etiology of TRD as well as the availability of new and effective therapies hopefully will decrease the morbidity and mortality associated with this condition.

KEY WORDS: Treatment resistant depression; antidepressant; atypical antipsychotic.

INTRODUCTION

Despite recent advances depression remains a challenge for the practicing clinician. Almost one third of patients with depression do not respond to monotherapy with an antidepressant. Treatment resistance confers an additional economic burden, resulting in higher treatment costs than those associated with the care of non–treatment-resistant patients.

PREVALANCE OF TRD

Estimates of TRD prevalence are lowest in primary care settings and progressively increase in outpatient psychiatry settings, inpatient psychiatric settings, and academic/tertiary care settings. Based on data from randomized controlled trials (RCTs) conducted in a research setting, Stage 1 TRD has a prevalence of ~50% when "response" is used as the criterion outcome and at least 60% when "remission" is used. Studies in clinical practice settings have reported even lower remission rates of 15% to 35%. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, conducted in both psychiatric and primary care practice settings, patients with nonpsychotic major depression (N=2876) were treated in Stage 1 for 12 weeks with citalopram at a mean final daily dose of 55 mg. Stage 1 response rates were 47% and remission rates were 28% [1] that suggests prevalence for Stage 1 TRD of ~50% using response criteria and of~70% using remission criteria. Recent STAR*D data reported response rates of 26% to 28% when switching to a second antidepressant (sustained release bupropion [N=239], sertraline [N=238], or venlafaxine-XR [N=250] after failure to achieve remission (or intolerance) with initial citalopram treatment[2]. Given a 12 month MDD prevalence estimated at 6.6%[3], the 12 month prevalence estimates are ~3% for Stage 1 TRD and ~2% for Stage 2 TRD. Adequately powered and well controlled trials of TRD in Stages 3 to 5 in clinical

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practice settings have not been reported, and thus no estimates are available.

DEFINITIONS

Depression is considered resistant or refractory when at least two trials with antidepressants from different pharmacologic classes (adequate in terms of dosage, duration, and compliance) fail to produce a significant clinical improvement[4]. An adequate response is defined as much or very much improvement on rating scales or 50% improvement in depression rating scale scores. Currently the recommended adequate dosages have increased from 150 mg daily to between 250 and 300 mg daily of imipramine or its equivalent[5]. Adequate duration of treatment also varied widely from 4 weeks to 12 weeks in different studies with number of Antidepressants taken for treatment resistant from 1 to 3, even upto 5. A TRD may be chronic, but a chronic depression is not necessarily resistant to treatment—for example, it may be that no treatment was attempted. TRD also may remit spontaneously, further differentiating the concepts of treatment resistance and chronicity.

- **Nonresponse:** A lack of response or response poor enough to require a change in treatment plan [e.g., failure to achieve 50% reduction in HAM-D score (or equivalent scale)].
- **Response:** Therapeutic response good enough to indicate continuing present treatment plan (e.g., 50% reduction in HAM-D score)
- **Remission :**Attainment of virtually asymptomatic status (e.g., HAM-D 7) for at least 2 consecutive weeks
- **Recovery:** Remission for 6 consecutive months.
- **Adequate antidepressant trial:** is defined as a trial in which an appropriate drug is given in a dosage and duration sufficient to produce a response. Nowadays, four to six weeks is considered an adequate trial period to see clinical response, although recent research suggests that longer periods of up to eight or 12 weeks may be needed to achieve remission.
- **Adequate dosage:** Clinically, it is defined as the minimum dosage that would produce the expected effect/ the maximum dosage that a patient can tolerate until the expected effect is achieved.
- **Pseudo-resistance:** Nonresponse to treatment that is inadequate in dosage and duration.
- **TRD:** Nonresponse despite two treatment trials with drugs from different pharmacologic classes, each used in an adequate dose for an adequate period. However, **t**here is no universally accepted definition of TRD. A review of ten years literature revealed more than 15 definitions[5]. One can approach these concepts from a categorical or a dimensional perspective.
- **The categorical approach** is based on the use of cutoff points. For example, some have proposed that depression should be considered resistant when two adequate trials of different antidepressants have failed, while others suggested a higher threshold that consisted of nonresponse to three or more adequate trials, one of which must have been a tricyclic.
- **The dimensional perspective** places a greater emphasis on levels of resistance and specifying the treatments to which the depression does not respond, rather than viewing resistance as an intransitive phenomenon.
- **Difficult-to-treat depression:** "includes depression that inherently does not respond satisfactorily to one or more treatments that are optimally delivered (TRD) and also depression treated under circumstances precluding the optimal delivery of potentially effective treatments. Such circumstances include the use of subtherapeutic doses, nonadherence, intolerable side effects that prevent an adequate dose or duration of treatment, and concurrent axis I, II, or III conditions that reduce the likelihood of remission for adherence, pharmacokinetic, or pharmacodynamic reasons."

NEUROBIOLOGY OF TRD

Major depressive disorder (MDD) is accompanied by alterations in serum, CSF or brain concentrations of excitatory amino acids such as aspartate and glutamate, and in serum concentrations of other amino acids, such as serine, glycine and taurine. Brain glutamate concentrations exceeding those normally are found in the synaptic clefts can cause selective neuronal loss and may be involved in a variety of chronic neurological disorders. NMDA subtype of glutamate receptors plays a role in the pathophysiology of depression. However no study has examined whether serum alterations in the amino acids are relevant to pathophysiology of TRD. There is only sparse literature examining the effect of ADs on amino acid concentration. One study found that CSF levels of glutamate and aspartate were not affected by ADs whereas serine levels significantly increased in CSF of patients treated with ADs. Another study reported that (i)there are no significant differences in serum levels of the amino acids measured between patients with TRD and controls (ii) there is a significant association between lower serum aspartate, asparagine, taurine, thereonine and serine levels than a non response to treatment with Antidepressants and (iii) treatment with ADs have significant effects on the serum levels of several of the above amino acid. Studies combining behavioural, molecular, and electrophysiological techniques reveal that certain aspects of depression result from maladaptive stress-induced neuroplastic changes in specific neural circuits.[6]

STAGING OF TRD

The classification of TRD in stages has been recently proposed where increasing resistance is equated with an increased failure to respond to antidepressant strategies. The rationale behind this approach is the clinical impression that the greater the degree of treatment resistance, the lower the probability of response to any new treatment.

Thase and Rush Staging Method[7]: This could be useful in the classification of TRD, although its predictive value with respect to treatment outcome has not been systematically assessed.

Thase and Rush Staging Method (Table 1)

Stage 0:	Any medication trials, to date, judged to be inadequate
Stage I:	Failure of at least 1 adequate trial of 1 major class of antidepressants
Stage II:	Failure of at least 2 adequate trials of at least 2 distinctly different classes of antidepressants
Stage III:	Stage II resistance plus failure of an adequate trial of a TCA
Stage IV:	Stage III resistance plus failure of an adequate trial of an MAOI
Stage V:	Stage IV resistance plus a course of bilateral electroconvulsive therapy

Massachusetts General Hospital Staging Method[8]: considers both the number of failed trials and the intensity or optimization of each trial but does not make assumptions regarding a hierarchy of antidepressant classes. This method generates a continuous variable reflecting the degree of resistance in depression (Table 2).

Table 2 Massachusetts General Hospital Staging Method

1	No response to each adequate (at least 6 weeks of an adequate dosage of an antidepressant) trial of a marketed antidepressant generates an overall score of resistance (1 point per trial)
2	Optimization of dose, optimization of duration, and augmentation or combination of each trial (based on the Massachusetts General Hospital or Antidepressant Treatment Response Questionnaire) increase the overall score (0.5 point per trial per optimization or strategy).
3.	Electroconvulsive therapy increases the overall score by 3 Points.

The European Staging Method: TRD is defined as a failure to respond to 2 adequate trials of different antidepressants given in adequate dosages for a period of 6 to 8 weeks.

A. **Nonresponder to**: TCA, SSRI, MAOI, SNRI, ECT, Other antidepressant(s)

No response to one adequate antidepressant trial

Duration of trial: 6–8 weeks

B. **TRD:** Resistance to 2 or more adequate antidepressant trials

Duration of trial(s):

TRD 1: 12–16 weeks

TRD 2: 18–24 weeks

TRD 3: 24–32 weeks

TRD 4: 30–40 weeks

TRD 5: 36 weeks–1 year

C. **Chronic resistant depression:** Resistance to several antidepressant trials, including augmentation strategy

Duration of trial(s): at least 12 months

ASSESMENT AND PREDICTORS OF RESISTANCE

A basic requirement in assessing resistance in depression is the accuracy of the diagnosis.It is important to assess the duration of the current trial and its interaction with the degree of response. As shown by Nierenberg et al (1995),[9] minimal response after 4 weeks of antidepressant treatment predicts poorer outcome at 8 weeks. These findings have challenged the utility of an 8 to12 week trial in someone with no early sign of improvement. Another important step toward the assessment of resistance in depression concerns the level of drug treatment adherence. Finally, clinicians need to use reliable measures of outcome in establishing resistance. While the use of clinician-rated instruments is preferred, it is more common for clinician to use clinician global assessments, often combined with self-rated instruments.

- **Predictors of Resistance to a Single Antidepressant Treatment**: The search of valid and robust predictors of resistance to a single antidepressant treatment has yielded inconsistent findings. It is also not clear if predictors are independent of the type of treatment.

Type of depression: Atypical depression is associated with poorer response to treatment with TCAs, but not SSRIs or MAOIs. Chronic forms of depression, such as index depressive episodes lasting two years or more or double depression is associated with poorer outcome.

Comorbidity: Substance abuse, and even moderate consumption of alcohol, is associated with poorer response to antidepressant treatment. MDD, with comorbid anxiety disorders, is also associated with poorer response to antidepressant treatment. Comorbid personality disorder is associated with poorer outcome in some. Neuroticism was associated with poorer antidepressant response in earlier studies, but not more recent ones [10]. Specific medical comorbidity (e.g., diabetes, coronary artery disease) has been associated with poorer outcome.

Decreased subjective social support, poorer social adjustment and interpersonal relationships have been associated with treatment resistance in some.Psychotic features in unipolar depression are associated with poorer treatment outcome following treatments with antidepressants alone. When such features are detected, the addition of antipsychotics is warranted. Finally, of course, failure to respond to multiple prior trials of antidepressants is often a significant predictor of poorer response to antidepressant treatment.

- **Predictors of Resistance to Multiple Antidepressant Trials or ECT**: Longer duration of the depressive episode and relatively greater personality disorder comorbidity were associated with poorer response to lithium augmentation. On the other hand, contradictory findings have been reported. Similarly, TRD patients did not differ in degree of Axis I psychiatric comorbidity from nonresistant depressed patients in one study.

CORRELATES OF TRD

There is the possibility of considering TRD as a unique subtype of depression as: (1) clinical characteristics

and course of TRD (behavioral phenotype), (2) neurobiological profile (EEG, neuroimaging, genetics, laboratory studies), and (3) the context and environment in which TRD develops. The identification of meaningful subtypes of depression is vital to those fields of psychiatric research that are beginning to establish that depressive disorders are brain diseases with unique genetic, neurophysiologic, and molecular features and that can eventually provide us with much-needed etiologic information on which to ground an ideal future classification system.

CLINICAL CHARACTERISTICS AND COURSE (Behavioral Phenotype): Several correlates for a worse outcome following an episode of major depression have been identified.

Atypical depression is characterized by mood reactivity, weight gain, increase in appetite, hypersomnia, interpersonal sensitivity, and leaden paralysis. Atypical depression may be relatively resistant to TCAs but show a good response to MAOIs and possibly to the SSRIs and bupropion.

Psychotic depression is characterized by the presence of either delusions or hallucinations, which are often but not always congruent with the depressive themes.

Bipolar depression: The response to treatment is often poor and the process of recovery is frequently slow. Some characteristics that distinguish bipolar depression from unipolar depression include age of onset, number of lifetime episodes, and gender distribution. A number of investigators have suggested a greater incidence of reverse vegetative signs (e.g., hypersomnia, increased appetite, weight gain) and have pointed to the relatively poor response to TCAs in this population. Lamotrigine and antidepressants, mainly SSRI's which have a lesser propensity for hypomania may be used.

Depression with psychiatric comorbidity, particularly anxiety, has been found to be associated with chronicity, poorer response to antidepressants, delayed response, greater severity of depression and anxiety, functional impairment, and decreased responsiveness to treatment. MDD with **comorbid panic disorder** is associated with greater chronicity and severity of anxiety and depressive symptoms, higher rate of suicide, higher risk of recurrence, and greater psychologic and psychosocial impairment than either disorder alone. A retrospective study on 1471 depressed patients found that a comorbid **personality disorder** is associated with a worse outcome. Several symptoms of **alcohol and substance** abuse can contribute to TRD.

Medical comorbidity represents another major factor of treatment resistance. Hypothyroidism, stroke, diabetes, coronary artery disease, Parkinson's disease, HIV infection, AIDS, cancer, and chronic pain can play a major role in inducing and sustaining TRD especially when the medical illness is irreversible. Some of the medications used to treat comormid medical conditions may induce or worsen a depressive episode. A number of other variables have been identified as indicators for nonresponse to antidepressants such as female gender and older age.

Neurobiological Profile: A number of possible biological correlates to depression, including TRD, have been described. Data from ECT, pharmacotherapy, and psychotherapy studies suggest that some EEG changes may be predictive of treatment nonresponse. Patients undergoing ECT treatment (because of TRD or of severe depression with psychotic features) tend to show: (1) severe sleep disruption with several arousals. (2) early awakening. (3) short rapid eye movement (REM) latency. (4) high REM density and (5) sleep-onset REM periods (first REM period within 20 min of falling asleep). Several of the characteristics mentioned (total sleep time, REM latency, and REM density) returned to normal after the ECT course, whereas sleep-onset REM periods (the first REM period within 20 min of falling asleep) did not. Also, a relationship was observed between the presence of sleep-onset REM periods after the course of ECT and poor response to, or a high rate of relapse after, ECT therapy. Shortened REM latency has also been reported for patients who fail to respond to psychosocial treatment.

Neuroimaging Findings: Several important findings suggesting the possibility that different topographies might be related to treatment response have been

described. Although neuroimaging studies have focused primarily on MDD in general rather than on TRD specifically, the findings may be usefully applied in refractory depression. A number of abnormalities have been found in depressed patients, including

- decreased glucose metabolism in the entire parietal lobe.
- increased metabolism in the superior posterior parts of the parietal lobe.
- decreased metabolism in the inferior part of the parietal lobe
- reduced glucose metabolism and hypofrontality bilaterally in the prefrontal cortex .
- decreased blood flow and metabolism in the subgenual prefrontal cortex.
- decreased blood flow or metabolism in the caudate nucleus.
- and decreased activity in the insula and in the temporal lobe.

Structural neuroimaging: Studies have suggested a relationship between TRD and:

- right frontostriatal atrophy,
- changes in the left hippocampus.
- reduction in the frontal lobe volumes,
- subcortical graymatter hyperintensities, and white matter hyperintensities.
- Negative correlations have been reported between chronicity of illness and ventricular-brain ratio, right temporal volume and amygdala-hippocampus volume.
- Several studies, most involving elderly depressed patients, have suggested that pathologic vascular changes (white or gray matter hyperintensities) may play an important role in treatment nonresponse and that vascular depression may be classified as a specific subtype of depression.

Genetics and Familial Patterns: Positive family history is associated with early age of onset of depression and with chronicity, which have both been linked to resistance. Patients with TRD are more likely to have a family history of affective illness in the first-degree relatives than patient without chronic depression. Candidate genes regularly include members of the main neurotransmitter systems such as serotonin, dopamine, and glutamate.

The serotonin transporter (5-HTT) is the selective site of action of several antidepressants and the 5-HTT gene is a strong candidate gene for affective disorders. Two extensively studied polymorphisms of the 5-HTT gene are the variable number of tandem repeats (VNTR) in the second intron and the 44 base pair insertion–deletion in the promoter region (5-HTT linked polymorphic region [5-HTTLPR], two alleles: l and s)[11]. Significant associations have been reported in patients with major depression between the 5-HTTLPR allele and the response to paroxetine[12,13], fluvoxamine[14], and total sleep deprivation. Associations with the response to paroxetine and fluvoxamine have also been described for the s allele of the 5-HTTLPR and for the ST in 2.12 allele in the VNTR[15]. However, other pathways that have influence over several neuroendocrine systems have recently received considerable attention. One such pathway, the hypothalamic– pituitary–adrenal (HPA) axis, plays a major role in stress hormone regulation. Several hypotheses that could link genetics to TRD have been formulated. For instance, it has been observed that genetically determined abnormalities in pharmacokinetics (medication absorption, transport, distribution, metabolism, and excretion) and pharmacodynamics (tissue response) can play a role producing vulnerabil ity to TRD.

Laboratory Findings: Laboratory variables associated with poor outcome of depressive episodes include blunted prolactin response to fenfluramine challenge, impairment in immune function and HPA axis overactivation. However, many of the results are still inconclusive. For instance, it has been observed that hypercortisolemia does not always predict acute antidepressant failure, despite the fact that it can be associated with severe symptoms such as insomnia, psychotic cognitive impairment, anxiety, agitation, and suicidality.

Context and Environment: Several "environmental" factors have been related to poor treatment outcome, including -

- lower socioeconomic status.
- nonsupportive social environment.
- family conflicts, chronic stressors , multiple loss events, lower levels of education and work dysfunction.

Nonadherence has been estimated to account for as many as 20% of cases considered to be treatment resistant and has been associated with younger age, unmarried status, and intolerance of side effects. Although nonadherent patients would be excluded from many of the currently used definitions of TRD, there is no doubt that they represent a group of difficult-to-treat patients who are unlikely to achieve complete remission.

ISSUES RELATED TO CHILDHOOD AND ADOLESCENCE

Comorbidity is the rule rather than exception in TRD children and adolescent. ADHD and dysthymic disorder is common along with comorbid anxiety disorder and disruptive disorder. Childhood sexual abuse and parental depression are significant factors[16]. IPT is useful to modify social and interpersonal functioning. Role of comorbid medical condition is also important. A significant risk factor is development of bipolar disorder. Geller et al.[17] reported 10-15% incidence of bipolar disorder in children. Before being given antidepressant the child should be properly evaluated for avoiding later development of bipolar disorder. Psychosocial issues and family environment should be addressed properly. Effect of CBT on psychosocial issue resolution is not clear. Nemaroff et al.[18] predicted good response to CBT. Kaminski and Graber[19] reported use of family therapy especially in parent child conflict and parental depression. But studies examining efficacy of combination treatment (pharmacotherapy and psychotherapy) in children have at the best modest benefits over pharmacotherapy alone[20]. In drug therapy, studies have shown a better response rate in adolescent than in children and adolescent tend to metabolize SSRI faster than adults. One study found that TCA shows no better effect than placebo in children. It was also corroborated in later studies. A controlled study found no significant active versus placebo response difference is present while others found a significant active versus placebo difference for SSRI. No clear recommendations exist for when to switch or augment.

ISSUES RELATED TO GERIATRIC RESISTANT DEPRESSION

There are few adequately controlled studies of TRD in geriatric population. Most of the studies focus on geriatric depression. Alexopolus et al.[21] described rate of medical comorbidity as high as 25-50%. A recent study[22] found anxiety among 67.0% of cases, medical burden on 43.6% of cases and significant cognitive impairment among 32.3% cases among TRD patients. Among 1/3 of patients who failed on initial antidepressant trial: augmentation strategies can not be prescribed due to comorbid medical condition. One must be careful not to view age related brain changes as necessarily pathoetiologic, as there is always a danger of mapping multiple colinear markers that may bring us no closer to effective treatments.

Evidences for efficacy of psychotherapeutic interventions in old age are few and most of the studies are based on evidences in old age depression. Even these studies were having difficulties. Scott et al.[23] studied 100 studies of effect of psychotherapy and its combination in late age depression found that, only 17 studies met minimum sample size of 25. Only 1 study followed up patients for 2 years. The data for frail elderly and older adults with cognitive impairments are nearly absent. The evidence for combined treatment in late life depression is still preliminary, although good results are reported in chronic or recurrent depression. Majority of research on late life depression found strong association with executive dysfunction, memory deficit, slowed information processing speed and visuospatial disturbances. No psychotherapy studies addressed these options particularly. SSRIs are now a

day preferred over TCAs but most of the studies shows comparable efficacy between two groups. Studies of SSRI alone or in combination with antipsychotic drugs in elderly psychotic depression are lacking and in absence of it, data available from more young population is generalized to older age group. In summary, the only strategies for 'resistant depression' in later life for which there is at least reasonable evidence are ECT and lithium augmentation, with prolongation of the standard course of antidepressant monotherapy as a third option for less severely depressed patients.

MANAGEMENT STRATEGIES FOR TREATMENT RESISTANT DEPRESSION

Strategies for the treatment of RD include optimization, substitution or switching, combination, and augmentation therapies. Currently there are no clear guidelines on when to substitute, combine, or augment therapies in the treatment of patients with TRD; however, management should follow a stepwise approach that allows treatment modification according to the response achieved. If a patient has a partial response, augmentation or combination therapies may be the most sensible strategy. If no clinical response is observed, switching may be indicated. With the exception of the STAR*D project, most of the literature on pharmacologic options focuses on short-term efficacy.

Optimization: Prescribing antidepressant medication in dosages that are too low and for lengths of time that are too short are common causes of treatment failure. Inadequate antidepressant dosage and duration are particularly prevalent in elderly patients. Some depressed patients who are resistant to treatment may benefit from antidepressant dosages that are higher than the usual recommendations.

Augmentation: Augmentation can be defined as the use of a psychotropic agent that does not have an indication for depression to enhance the effect of an antidepressant. The theoretical rationale of augmentation is to obtain a different neurochemical effect by adding an agent affecting different neurotransmitter systems. Additionally, an augmentation agent can be used to broaden the therapeutic effect (eg, by adding an antianxiety agent to an antidepressant).

- **Lithium:** Among the most widely studied augmentation agents is lithium augmentation (>600 mg/d) of TCAs, MAOIs, and SSRIs. It apparently enhances serotonin transmission by reducing the activity of post-synaptic serotonin receptors. This, in turn, reduces the negative feedback to serotonin-releasing cells and thereby increases serotonin levels in the synaptic cleft. Lithium may also have effects on other neurotransmitter systems and neuromodulators. A starting dosage of 150 mg twice daily, with a trough serum level obtained within one week, is a practical starting point for augmentation therapy. The lithium dosage should be adjusted to result in a serum blood level between 0.4 and 0.8 mEq per L (0.4 and 0.8 mmol/L). In clinical practice, aiming for the lower limit is prudent, since there is probably equal augmentative efficacy at serum blood levels of 0.4 and 0.8 mEq per L (0.4 and 0.8 mmol per L). Attempting to enhance response by increasing the dosage to higher serum blood levels may only result in unwanted side effects[24].
- **Thyroid hormone augmentation:** Triiodothyronine (T_3) appears to be a more effective augmentation agent than tetraiodothyronine (T_4) and is effective in small dosages; for example, 25 to 50 μg per day. T_3 may be used to augment response to tricyclic antidepressants, monoamine oxidase inhibitors and SSRIs. Beyond the observation that T_3 potentiates noradrenergic activity, its mechanism of action as an augmentation agent is not clearly understood. Although fewer controlled studies have focused on thyroid hormone than on lithium, T_3 augmentation of TCAs has been shown to be effective in approximately 50 to 60 percent of patients.
- **Buspirone,** a 5-HT_{1A} partial agonist, augment SSRIs by blunting the negative feedback of increased synaptic serotonin effects on the presynaptic 5-HT_{1A} receptor. The STAR*D study compared buspirone with bupropion and found

that both helped about 30% of patients who had not reached remission[25]. One particular advantage of buspirone is that it may be helpful in SSRI-induced sexual dysfunction among women.

- **Pindolol.** The 5-HT_{1A} postsynaptic antagonist pindolol accelerates the onset of action of antidepressants by preventing negative feedback to the presynaptic 5-HT_{1A} receptor which results in higher levels of 5-HT in the synapse. Pindolol, at dosages of 2.5 to 7.5 mg per day for a trial period of up to six weeks, might prove to be an effective augmentor of SSRIs.
- **Dopaminergic agonists** have been particularly interesting because they bring in a mechanism of action missing from antidepressants. Pergolide (0.25–2 mg/d), amantadine (100–200 mg twice daily), pramipexole (0.125–1 mg three times daily), and ropinirole (0.5–1.75 mg twice daily) have been found to be helpful in uncontrolled studies in patients who had MDD. Disadvantages include the side of effect of nausea (with the older compounds) and a lack of controlled studies. An advantage is that pramipexole, ropinirole, and amantadine have been used to treat SSRI-induced sexual dysfunction. Pramipexole and amantadine also may have neuroprotective properties[26], consistent with the neuroprotective or neurogenesis hypothesis of antidepressant action[27].
- **Traditional psychostimulants** that affect dopamine as potential augmenting agents include methylphenidate (10–40 mg/d) and dextroamphetamine (5–20 mg/d). Their use has been reported as augmentation of TCAs, MAOIs, and SSRIs. The only two controlled trials in TRD were negative[28], and clinicians also may avoid using them because of the potential for abuse by patients who have a history of substance abuse, a frequent comorbid condition with MDD[29]. On the other hand, ADHD is a frequent comorbid condition of MDD, and a psychostimulant therefore could be quite helpful.
- **Modafinil**: A few open trials suggested the efficacy of modafinil (in doses up to 400 mg/d). A double-blind study was positive for the treatment of residual fatigue and sleepiness on SSRIs[30], but its efficacy is unclear in patients who do not experience fatigue and sleepiness.
- **Folate and related compounds:** These participate in the transfer of methyl groups involved in neurotransmitter synthesis and DNA regulation. Open augmentation with methylfolate (15–30 mg/d) resulted in a statistically significant improvement in depression scores in one study. Open addition of s-adenosylmethionine (SAMe, 800–1600 mg/d) also had promise.
- **Anticonvulsants:** Lamotrigine (100–300 mg/d), gabapentin (300–1800 mg/d), topiramate (100–300 mg/d), carbamazepine (200–400 mg/d), and valproic acid (500–1000 mg/d) have been studied as augmentation agents. Disadvantages of this approach include potential tolerability issues with some of the anticonvulsants (eg, sedation or weight gain) and the specific risk of Steven Johnson's syndrome with lamotrigine and carbamazepine that necessitates a slow dose escalation. A potential advantage is that anticonvulsants may help mitigate anxiety symptoms.
- **Benzodiazepines** may treat anxiety and also help with core depressive symptoms when added to an antidepressant. Evidence exists for the efficacy of lormetazepam in a double-blind, placebo-controlled augmentation study of TCAs. Clonazepam also was nonsignificantly superior to placebo in augmenting fluoxetine, and zolpidem was better than placebo in augmenting SSRIs for sleep problems but not depression. The disadvantages include potential sedation and, in the case of benzodiazepines, the possibility of abuse.
- **Riluzole**, a putative antiglutamatergic agent indicated for the treatment of amyotrophic lateral sclerosis, as add-on therapy for treatment-resistant major depressive disorder.

Other augmentation agents have been added to failed trials of antidepressants, but none have been studied extensively. Inositol (up to 12 g/d) was found to be no better than placebo in a double-

blind study. Evidence for the opiates oxymorphone and buprenorphine is mostly anecdotal. A small, positive double-blind study supported the use of dehydroepiandrosterone (up to 90 mg/d). Gonadal hormones have limited support. One small, double-blind study reported positive results from the use of testosterone gel (1% gel, 10 g/d) in men, and estrogen has limited support from mostly anecdotal evidence.

Combinations

- **SSRI plus bupropion**: Despite its popularity, the evidence for the efficacy of this combination is minimal. Open trials of bupropion (150 mg SR/XL daily or twice daily) initially suggested that this combination would be helpful. In a small trial, 54% of 28 partial and nonresponders to SSRIs or venlafaxine responded to an open-label trial of bupropion SR augmentation. A disadvantage of combining SSRIs or SNRIs with bupropion is tremor. Advantages are the theoretical gain of effecting changes in the dopamine, serotonin, and norepinephrine systems and that the addition of bupropion may help manage SSRI-induced sexual dysfunction. Among citalopram nonresponders in level 2 of the STAR*D study, bupropion combined with citalopram was nonsignificantly more effective than buspirone augmentation[25].
- **Mirtazapine with SSRIs**: Another intriguing combination of theoretical interest is the dovetailing combination of mirtazapine with SSRIs or with SNRIs. In a placebo-controlled trial of mirtazapine (15–30 mg at night) plus SSRIs, more patients improved with the combination than with placebo addition. The considerable promise of the combination resulted in mirtazapine plus the SNRI venlafaxine as being used one of the two treatment options in level 4 of the STAR*D study, in which this combination showed a nonsignificant advantage over tranylcypromine[31]. Disadvantages are the weight gain and sedation associated with the antihistaminergic effects of mirtazapine. Advantages are that mirtazapine plus SSRI should be synergistic: because of its alpha-2 antagonist properties and 5-HT2 and 5-HT3 receptor blocking, mirtazapine could decrease the adverse effects (nausea, anxiety, and sexual dysfunction) caused by SSRI stimulation of these receptors.
- In small case series the addition of **trazodone or nefazodone to SSRIs** was found to result in a positive response rate in patients who had TRD. Disadvantages include somnolence (trazodone) and risk of hepatotoxicity (nefazodone). An advantage is that trazodone and nefazodone may help insomnia.
- The combination of **SSRIs and TCAs** was first reported in 1991 with fluoxetine and desipramine (25–75 mg/d). Disadvantages are that several SSRIs inhibit the CYP450-2D6 system, and TCAs are substrates of this liver isoenzyme, resulting in increased blood levels of the TCA that can cause more adverse effects or toxicity. Another problem is that low response rates were found in two double-blind studies. There is evidence, however, that this combination may produce a more rapid onset of action. Also, remission rates were significantly higher with desipramine plus fluoxetine than with either drug alone.
- Similar to the **combination of SSRIs NARI (reboxetine)** (8–12 mg/d), has shown some promise in combination with SSRIs. Atomoxitin (40–120 mg/d), a norepinephrine reuptake inhibitor (NRI) approved for the treatment of ADHD, was found to be no better than placebo in a large, double-blind trial of TRD. Combining a 5-HT uptake inhibitor and a norepinephrine uptake inhibitor may be useful in severely depressed patients. Also, these NRIs have better safety and tolerability than TCAs.

Switching Pharmacotherapy

If a treatment fails, either because of lack of efficacy or intolerable adverse effects, it makes clinical sense to switch to an alternative treatment. Several choices exist: switching to an alternative pharmacotherapy, switching to an evidence-based psychotherapy, or switching to a neurotherapeutic device that delivers

energy to the brain. Switches can be classified as within or outside of class. Within-class switching has the pharmacologic rationale that each medication shares a common mechanism of action, but each has its own pharmacologic ''fingerprint'' with differential effects on other neurotransmitters and receptors. Outside-of-class switching is done with the hope that changing the primary mechanism of action will prove more effective.

- **Switching from one SSRI to another** is supported by open trials of ''historical failures,'' showing 50% to 60% response rates when switching from other SSRIs to citalopram[32], from sertraline to fluoxetine, or from one SSRI to another. Switching from one SSRI to another may be less effective than switching to a non-SSRI, as suggested by a double-blind study of a switch to paroxetine versus a switch to venlafaxine. The results of level 2 of the STAR*D study showed no significant advantage of switching to a non- SSRI compared with a same-class switch in subjects who had not responded to treatment with one SSRI (citalopram)[2]. An advantage is that the immediate switch from one SSRI to another seems to be well tolerated. Switching from a TCA to a SSRI is an option that has not received extensive coverage in the literature. The disadvantage of a switch to a SSRI is the well-known high rate of sexual dysfunction in persons treated with SSRIs. An advantage of a SSRI over a TCA is that SSRIs typically are better tolerated than TCAs.
- **Switching to SNRIs** is certainly a reasonable option in TRD. An open study showed 30% to 33% of 84 consecutive patients who had TRD (defined as having not responded to three or more trials) responded to 12 weeks of open treatment with the SNRI venlafaxine (300–450 mg/d). Similarly, 58% of 152 depressed patients who had not responded to one previous antidepressant trial responded to an 8-week open venlafaxine treatment (75–375 mg/d). In a larger study, 52.6% of 312 depressed patients who had either ''absolute'' or ''relative'' treatment resistance responded to open venlafaxine treatment. Finally, about 69% of 69 SSRI-resistant depressed patients were considered as responders after venlafaxine treatment. Even though a doubleblind study found that switching to venlafaxine was significantly superior to a switch to paroxetine in patients who had TRD, the results of level 2 of the STAR*D study did not show any significant advantage of switching citalopram nonresponders to venlafaxine as compared with sertraline[2]. Disadvantages of venlafaxine are blood pressure elevations at higher doses and discontinuation reactions with sudden discontinuation. An advantage is that venlafaxine may be more effective than SSRIs in severe or melancholic depression.
- **Switching to mirtazapine** is yet another option. Forty-seven percent of patients who had not responded to or tolerated SSRIs showed response to mirtazapine (15–45 mg/d), and 38% responded in another study when patients either were switched to mirtazapine or added it to ongoing medication. The disadvantages of mirtazapine are the adverse effects of sedation and weight gain. The advantages of mirtazapine are that, by blocking 5-HT2 and 5-HT3 receptors, mirtazapine may prevent SSRI discontinuation–emergent adverse events, and immediate switching seems to be well tolerated.
- **Switching to bupropion** is an opportunity to expose patients to the novel dual mechanism of norepinephrine and dopamine uptake inhibition. Among 30 TCA nonresponders, bupropion was better than placebo in reducing depressive symptoms. Sixtyone patients who had not responded to at least one antidepressant and who then took either citalopram or bupropion for 6 weeks and did not respond were switched to the alternative medication or to citalopram combined with bupropion. Switching resulted in a remission rate of 7%; 28% reached remission with the combination. A disadvantage of switching from an SSRI to bupropion is that SSRI-induced discontinuation reactions may occur. An advantage

is that a switch to bupropion reduces the incidence of weight gain and sexual dysfunction associated with SSRIs.

- **SSRI to TCA**: Clinical lore suggests that the older generation of TCAs may have greater efficacy than SSRIs, but the literature on such a switch is small. A few studies found some efficacy with a switch to a TCA in patients who had TRD and in SSRI nonresponders. The disadvantages are the usual side effects and toxicity caused by TCAs: sedation, anticholinergic side effects, weight gain, and lethality in overdose. Advantages include a clear dose–response curve, the low cost of some of the generic TCAs, and possible superiority of some TCAs compared with SSRIs in severe/melancholic depression.
- **Nefazodone and trazodone** are two antidepressants that are used frequently for insomnia. In terms of switching, a retrospective study of 20 depressed patients who had not responded to or tolerated prior antidepressant treatment suggested the usefulness of trazodone. Patients who had discontinued an SSRI because of ''poor response'' showed significant improvement with nefazodone (300–600 mg/d). The disadvantages are that these medications frequently are underdosed, and nefazodone requires twice-daily dosing. Furthermore, nefazodone has a black box warning because of the risk of fatal hepatic toxicity. Advantages include less weight gain and sexual dysfunction than seen with SSRIs.
- **MAOIs** are used less frequently but also can be considered as alternative agents for switching. In one study of patients who had not responded to imipramine, 58% to 65% showed improvement with MAOIs. Disadvantages include dietary restrictions, risk of hypertensive crises and serotonin syndromes, and the need for wash-outs before starting and after ending treatment. Advantages are that the MAOIs are useful in atypical unipolar depression and anergic bipolar depression. The considerable promise of the MAOIs in TRD resulted in the choice of tranylcypromine as one of the two treatment options in level 4 of the STAR*D study, in which it was found to be nonsignificantly less effective than the mirtazapine/venlafaxine combination [31].
- The **norepinephrine uptake inhibitors** reboxetine (4–10 mg/d) and atomoxetine (40–120 mg/d) also may have some usefulness as switching agents. In one study, patients who had not responded to an adequate trial with fluoxetine showed significant improvement with open reboxetine (8–10 mg/d). Disadvantages are that switching from an SSRI with a short half-life requires tapering and that no studies with atomoxetine have been reported in TRD. Advantages are that the norepinephrine uptake inhibitors are potentially useful in SSRI nonresponders who have a history of prior TCA response and perhaps in patients who have MDD with comorbid ADHD.

PROMISING NEW TREATMENTS

Some new and novel therapies show promise for the future treatment of TRD. These include new approaches to augmentation treatment, eg, addition of an atypical antipsychotic to the initial antidepressant; newer pharmacologic interventions; and nonpharmacologic therapies such as VNS, rTMS and DBS.

Augmentation Therapy: Atypical Antipsychotics and Antidepressants: Evidence suggests that risperidone (0.5–2 mg/d), olanzapine (5–20 mg/d), ziprasidone (40–80 mg twice daily), quetiapine (25–300 mg/d) and aripiprazole (15–30 mg/d) could be efficacious as augmentation agents in TRD. The benefits of augmentation with atypical agents, especially newer agents such as risperidone and olanzapine, include lower risk for extrapyramidal symptoms and tardive dyskinesia than with standard agents also these drugs may help manage anxiety and agitation.

Risperidone Augmentation of SSRI Therapy: At low doses, risperidone antagonizes the serotonin (5-HT)2A receptor—approximately 100 times more

effectively than the dopamine (D2) receptor. Because the 5-HT2A receptor acts in opposition to the 5-HT1A receptor, its inhibition may enhance the effects of serotonin at the 5-HT1A receptor and, thus, augment the effects of SSRI therapy. The potential benefits of augmenting SSRI with risperidone indicate the need for a controlled study.

Olanzapine Augmentation of SSRI Therapy: Olanzapine is similar to risperidone in that it binds with high affinity and antagonizes several receptor subtypes—dopamine (D1¡5), serotonin (5-HT2A,B,C), alpha 1-adrenergic, histamine (H1), and muscarinic (M1¡5) receptors. Yet, olanzapine differs from risperidone by its higher affinity for the 5-HT2C receptor and, in contrast to risperidone, possesses higher affinity for alpha 1- than for alpha 2-adrenoceptors. In a blinded comparative study, olanzapine demonstrated significantly greater efficacy in treating depression in patients with schizophrenia than did haloperidol. Most (57%) of these effects on mood were primarily direct effects of olanzapine. The investigators suggest that pharmacodynamic synergy between fluoxetine and olanzapine may cause a larger rise in norepinephrine and dopamine levels than that occurring with fluoxetine monotherapy. The robust and persistent increase in neurotransmitter release achieved with fluoxetine plus olanzapine suggests a unique synergy between these two agents. This synergy indicates a possible therapeutic mechanism for patients with TRD: specific targeting of dopamine-innervated prefrontal regions along with noradrenergic and serotonergic enhancement. This multimodal profile is a novel approach to TRD and one not observed with other augmentation strategies. Coupled with the encouraging results of the randomized, controlled clinical study, these insights indicate that effective augmentation therapy may be achieved with olanzapine and fluoxetine.

Quetiapine: An antagonist of 5-HT_{1A}, 5-HT_2, D_1, D_2, H_1, á1 and á2 receptors, it has no appreciable affinity at cholinergic musca-rinic and benzodiazepine receptors. Quetiapine is known to have a positive effect on depressive mood in patients with schizophrenia and bipolar dis-order.

Ziprasidone: exhibits high in vitro binding affinity for the D_2, D_3, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1D}, and á1 adrenergic receptors, and moderate affinity for the H_1 receptor. Ziprasidone func-tions as an antagonist at the D_2, 5-HT_{2A}, and 5-HT_{1D} receptors, and as an agonist at the 5-HT_{1A} receptor. Ziprasidone inhibits synaptic reuptake of 5-HT and norepinephrine. Dunner **et al.**[33] compared ziprasidone/sertraline with sertraline monotherapy in patients resistant to 6 weeks sertraline therapy and 4 their SSRI therapy. In this study, 50% responded and weeks of prior therapy with at least one SSRI or non-SSRI antidepressant. Patients who prior received a non-SSRI therapy demonstrated under augmentation with ziprasidone a significantly greater improvement compared with those patients who received sertraline monotherapy. Among patients with a history of SSRI resistance only, improvement with the combination therapy did not reach significance versus sertraline monotherapy. The second small study[34] was performed in 20 patients who received ziprasidone in addition to 28% achieved remission after 6 weeks of therapy.

Zotepine: has a high affinity for D_1, D_2, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors. Furthermore, it inhibits the reuptake of noradrena-line. Zotepine has been shown to be effective in the treatment of delusional depression in combina-tion with a TCA or SSRI. No data are currently available for treatment of TRD. However, like with quetiapine the latter studies might be indicative for the effectiveness in TRD.

Amisulpride: a selective antagonist for dopamine D2 & D3 receptors acts preferentially on pre-synaptic receptors increasing dopaminergic trans-mission at low doses. A placebo-controlled trial showed that amisulpride at a low dose (50 mg/day) is effective in the treatment of primary dysthymia.

SOMATIC THERAPIES FOR TRD

ECT: The efficacy of ECT for depression has been demonstrated in a large number of clinical trials. A recent metaanalysis found that real ECT was significantly more effective than simulated ECT (six trials, 256 patients), and treatment with ECT was

significantly more effective than pharmacotherapy (18 trials, 1144 patients). Bilateral ECT was more effective than unipolar ECT (22 trials, 1408 participants) [35]. Patients often require continued maintenance treatment; however, significant side effects such as memory loss are associated with ECT.

Ablative Limbic System Surgery: Neurosurgical procedures for treatment of psychiatric disorders include anterior cingulotomy, subcaudate tractotomy, limbic leucotomy, and anterior capsulotomy. These procedures have been found to be efficacious in patients suffering from intractable mood and anxiety disorders with response rates ranging from 35% to 70% over a period of several weeks to several months, depending upon the response criteria.

Vagus Nerve Stimulation: Evidence supporting a role for VNS therapy in depression came from early observations of mood improvement in patients with epilepsy who participated in early VNS studies.Prospective evaluation of epilepsy patients evaluated with standard depression symptom severity rating scales revealed that VNS therapy was associated with statistically significant improvements in mood that was not related to reductions in seizure frequency. The documented efficacy of anticonvulsants, such as carbamazepine, lamotrigine, valproate, and perhaps others, as mood stabilizers and/or antidepressants in bipolar disorder and the anticonvulsant properties of ECT are concordant with the hypothesis that VNS therapy may be a useful therapeutic option for depression. VNS results in markedly increased c-fos expression in forebrain (lateral hypothalamus, paraventricular nuclei, CA3 hippocampal fields, and neocortex) and brain stem regions (NTS, nucleus raphe magnus, PBN, A7 area, locus ceruleus, and periaqueductal gray), resolution of some of the regional cerebral blood flow (rCBF) abnormalities in limbic and cortical structures (eg insula, dorsolateral prefrontal cortex (DLPFC), temporal cortex) that are associated with depression[36].

Transcranial Magnetic Stimulation: The most used rTMS strategy for the treatment of depression is high-frequency rTMS (20-HZ) of the left DLPFC, but this strategy has an important cost benefit ratio and it may increase the risk of seizure. Therefore, lower frequency rTMS (1-HZ) strategies are potentially advantageous if clinical efficacy can be demonstrated. The rationale of targeting the left DLPFC is that lesion and imaging studies show that left prefrontal cortex dysfunction is pathophysiologically linked to primary and secondary depression. Because this dysfunction is associated with a decrease in the left DLPFC activity, high-frequency rTMS is used as it induces larger cerebral blood flow in the stimulated area in the majority of subjects[37]. Indeed, the vast majority of the initial rTMS studies applied high-frequency rTMS on the left DLPFC. It has been speculated that an inhibition of the right prefrontal cortex (based on the inhibitory effects of 1 Hz rTMS and the notion of laterality in prefrontal activity in depression) might correct the interhemispheric imbalance of DLPFC activity in depression. In a sham controlled blind trial by Fitzgerald et al.[38] in TRD patients found at the end of study that 44% of patients in active group and 8% of patients in sham group responded ($p<0.05$).

Magnetic Seizure Therapy: MST or convulsive rTMS refers to the administration of rTMS to the scalp to induce seizures under general anesthesia. Hypothetically, such magnetically induced seizures can replace ECT (and its associated adverse cognitive effects) in patients with TRD. The feasibility of the procedure has been demonstrated in a female subject with a 3-year episode of TRD[39]. A decrease in the HAM-D score from 20 to 13 was noted in the latter following MST. A randomized, controlled trial examined the procedure in eight patients with a major depressive episode who were candidates for ECT and found the procedure to be well tolerated[40]. The clinical efficacy of MST in the treatment of TRD and whether MST will be preferable to ECT remains to be established.

Deep Brain Stimulation: In one clinical trial of DBS[41] electrodes were placed in the subgenual cingulate cortex (approximately Brodmann area 25) bilaterally in six patients who had TRD. At 6 months, four of the six patients were classified as responders. Depressive symptoms also improved in the cohort of patients who

had intractable obsessive-compulsive disorder undergoing DBS[42]. Clinical trials of DBS in the anterior limb of the internal capsule for major depression are currently underway. To date, this procedure remains an experimental, not approved for general clinical use for this indication.

Natural Remedies

St. Johns wort: There are 37 published trials including 26 placebo controlled studies and 14 with standard antidepressant as the active comparator, but none of these focussed on TRD.

S-Adenosyl Mehionine: There are 45 published clinical studies for treatment of depression out of which 8 are placebo controlled and used an active comparator but very few for TRD. One study examined the efficacy of sAMe as an adjunct for partial and non responders to SSRI and found response and remission rates of 50% and 43% respectively and treatment was well tolerated. But still no published studies using placebo control is available.

Omega 3 fatty acids: A randomized, placebo controlled dose finding study of Eicosapentanoate (EPA) as adjunctive therapy with inadequate response on antidepressant trial reported that 1 gm/day of EPA for 12 weeks showed response rate of 53% compared to placebo of 29% with notable improvement of depressed mood, anxiety, sleep disturbance, libido suicidality[43].

ROLE OF PSYCHOTHERAPY

Interpersonal, cognitive, and behavioral therapies offer structured pragmatic methods to evaluate and work with such difficult patients. Although some evidence supports the use of these psychotherapies alone for treatment-resistant depression (in lieu of further trials of medication), data are emerging to suggest a potentially more valuable role when they are combined with pharmacotherapy. The newer depression-focused psychotherapies are relevant and potentially valuable strategies for patients with treatment resistant depression.

Evidence that psychotherapy works: Much of the evidence about the effectiveness of newer antidepressants comes from studies either supported by or directly conducted by the manufactures of those medications. A large portion of these studies are already convincing evidence that the new treatment works, at least in comparison to placebo. Since psychotherapy is not manufactured nor protected by patents, there are no comparable corporate research and development funds to sponsor research. Moreover, a pill placebo group is not an adequate control group for psychotherapy research. As a result, there will never be the weight of evidence supporting the efficacy of psychotherapy that can be marshaled for antidepressant pharmacotherapy. Nevertheless, a sizeable number of comparative studies have examined cognitive, behavioural and interpersonal therapies in relatively uncomplicated (without severe personality problems or a large number of comorbidities) groups of depressed outpatients and in aggregate, 4 conclusions can be drawn.

1. Depressions focused psychotherapies (i.e. cognitive, interpersonal, and behavioural therapies), typically provided across 8 to 16 weeks, are significantly more effective than waiting list or minimal contact control conditions.
2. Depression-focused therapies typically produse response rate comparable to those found with antidepressant medications in randomize clinical trials.
3. There is no compelling evidence that one form of depression focused psychotherapy is superior to another. It has been suggested that cognitive therapy may have more enduring effects following termination of therapy, but one controlled trial directly comparing cognitive therapy and interpersonal therapy did not reveal any advantage for the cognitive therapy condition across a 24 month follow up.
4. The addition of cognitive therapy or interpersonal therapy to ongoing pharmacotherapy increases the likelihood of remission for patients with chronic, severe recurrent or resistant or partially treatment

responsive treatment resistant depression thus represents an important indication for combining psychotherapy and pharmacotherapy.

Suggested guidelines for psychotherapeutic intervention for treatment resistant depression The therapy relationship should be collaborative and centered around the goal of teaching new skills to improve coping with a chronic illness. The therapist must pair core therapeutic skills (e.g. empathy and understanding) with the ability to appropriately select specific, targeted interventions (e.g. relaxation training, activity scheduling, problem solving, or cognitive restructuring).

- The therapist may make judicious use of examples from other medical models in which rehabilitative interventions are used to enhance the outcome of a chronic disorder (e.g. poststroke rehabilitation, pain management, or orthopedic rehabilitation).
- The therapist may express cautious optimism that problems can be addressed with varying degrees of success. However, it is important to be understanding of the patient's pessimism and elicit feedback from the patient about what has not worked well in the past.
- Establish stepwise, short term goals specifically addressing life problems and/or symptoms. Use graded tasks or intermediate assignments to approach more daunting or potentially overwhelming problems.
- Meet frequently and, if necessary, shorten sessions to enhance learning and retention. Keep sessions active and avoid the "silent treatment. Obtain feedback at beginning and end of treatment sessions so that patient's reactions to therapy can be monitored and promptly addressed. Be vigilant concerning subtle affective and behavioural reactions within sessions as an in vivo source of feedback.
- Use homework assignments and in session rehearsal to facilitate development of new coping skills. It is important to avoid implicit criticisms about difficulties in therapy, such as homework noncompliance. The therapist must address his or her own dysfunctional cognitions blaming the patient for "not wanting to get better".
- Involve spouse or significant others to provide psychoeducation and enhance alliance with family members.
- Establish intermediate and long term goals as symptomatic improvement and short term goals are accomplished.
- Do not terminate therapy until the patient has achieved a remission and sustained it for at least 4 to 6 months.

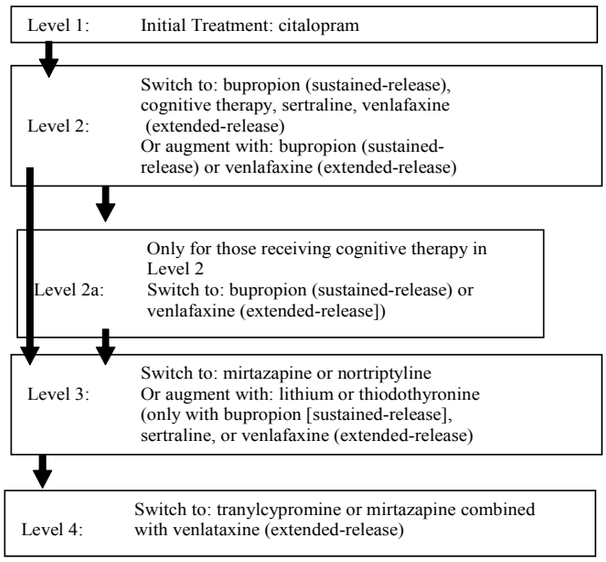
Managing the course of Therapy: The depression focused psychotherapies are conducted in both individual and group formats and typically range from 10 to 16 weeks in duration. Individual sessions are typically 45 to 60 minutes in length, whereas group sessions are usually 90 to 120 minutes long. Ideally, we would recommend twice weekly sessions early on to facilitate the process of therapy. Perhaps even more frequent sessions would be helpful, but economic considerataions usually make this impossible. We prefer to continue with twice weekly sessions until the patient has achieved at least a 50% reduction in symptom severity, shifting to weekly sessions thereafter. If the patient has not obtained significant symptom relief by the eighth week (i.e., 16th session), a careful evaluation of the continued indications for psychotherapy, as well as possible alternatives, should be undertaken. A successful course of acute phase, focused psychotherapy for treatment resistant depression typically lasts 4 to 6 months. It appears that patients who did not remit fully may benefit from less frequent, continuation phase sessions over the next 6 to 9 months.

SEQUENCED TREATMENT ALTERNATIVES TO RELIEVE DEPRESSION (STAR*D)

This study aims at determining the best subsequent treatment strategies (i.e. identifying which combinations and which sequences of treatment are effective with minimal side effects). This multisite, prospective, sequentially randomized controlled trial targeted 4000 adults with nonpsychotic major depressive disorder. Following treatment failure at each

of the 4 sequential levels, patients progressed to the next level, where they were randomly assigned to the various treatment options (Figure 1). Independent evaluators, blinded to level and treatment, conducted periodic clinical outcome assessments. These additional results will provide information on symptom severity, level of functioning, adverse effect burden, patient satisfaction/quality of lif, and health care utilization and cost. Once patients have obtained a satisfactory response, follow up assessment will determine the degree and timing of possible relapse.

Fig.1. The four sequential levels of STAR*D study



The remission rates for step one was 36.8%, for step two 30.6%, for steps three 13.7% and step four 13.0%. Remission rate declined significantly after step two. This might support the developing notion that treatment resistant depression can be defined by two prior treatment failure. High remission rates during initial trial were seen in patients who were female, employed or higher level of education and income. The cause of declining remission may be that the remission occurring due to nonspecific effects of patient care, attention, care, reassurance, education and can be called as placebo response, was declining. Khan et al.[44] showed that about 73% decrease in HDRS score in the drug group could be accounted by these factors. Rate of relapse increases with each step 33.5%, 47.4%, 42.9%, 50.0%. Relapse was even higher in patients who improved but did not achieved remission. Intolerance rate increased after each treatment step. 16.3%, 19.5%, 25.6%, 34.1%. Cumulative sustained recovery was calculated at 43% taking relapse into account and it does not include patients opting out. It pastes a little grim picture in outcome of TRD. Randomizataion was not done at step 2. Only 1.5% of patients agreed for randomization, so comparison between treatment strategies is difficult.It was found later on that patients entering cognitive therapy were having lower entry scores. It may explain the higher remission rate. According to Rush et al.[2] the biggest surprise of this study was comparable findings to SSRI-SSRI switch to switch to Bupropion or velafexine. Questions were raised weather longer duration of treatment is just as important to choosing a drug.

The drawbacks of this study are: (1) Only outpatient seeking medical care is included (2) Age limit was restricted to 10-75 (3) Patents with bipolar and psychotic disorder excluded (4) reliance on self report QIDS-SR16 as primary outcome (5) neither clinician nor participants were blind to treatment (6) placebo control was not used (7) dropout rate was quite high and most of the people who exited were not in remission (8) very high quality of care was delivered which may limit its generalibility.

CONCLUSION

Despite the numerous options available for the treatment of depression, many patients do not achieve a partial or full response with an adequate dose of two or more medications of different antidepressant classes, each given for a sufficient duration. Such resistance to psychopharmacologic treatment options challenges the practitioner. A staged approach to TRD includes reevaluation of the initial diagnosis and, when no correctable cause for TRD is found, optimization of the initial regimen. Other pharmacologic treatment approaches include switching antidepressant agents, adding a second antidepressant with a different

mechanism of action, and augmenting the effects of the initial antidepressant by adding an agent other than an antidepressant. Although this treatment paradigm provides several management alternatives, depression in many patients remains resistant. Promising new therapies now under investigation may soon be validated and available for use in clinical practice. Efforts to identify true TRD and its definitive clinical diagnostic criteria continue. A better understanding of TRD and the many facets of its etiology, as well as the availability of new and effective therapies, hopefully will decrease the morbidity and mortality associated with depression.

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