Tackling Partial Response to Depression Treatment

This ACADEMIC HIGHLIGHTS section of The Primary Companion to The Journal of Clinical Psychiatry *presents the highlights of the planning teleconference series "Tackling Partial Remission to Depression Treatment," which was held in March and April 2009. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Bristol-Myers Squibb Company and Otsuka America Pharmaceutical, Inc.*

The teleconference was chaired by ***Michael E. Thase****, MD, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia Veterans Affairs Medical Center, and Pittsburgh Medical Center, Philadelphia and Pittsburgh. The faculty were* ***Bradley Gaynes****, MD, Department of Psychiatry and the UNC Regional Center for STAR*D, University of North Carolina School of Medicine, Chapel Hill;* ***George I. Papakostas****, MD, Department of Psychiatry, Harvard Medical School and Massachusetts General Hospital, Boston;* ***Richard C. Shelton****, MD, Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, Tennessee; and* ***Madhukar H. Trivedi****, MD, Mood Disorders Research Program and Clinic, Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas.*

Financial disclosure: ***Dr Thase*** *is a consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Janssen, MedAvante, Neuronetics, Novartis, Pfizer, Schering-Plough, Sepracor, Shire US, Supernus, Transcept, and Wyeth-Ayerst; currently is a member of the speakers' bureaus for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, and Wyeth-Ayerst; has equity holdings in MedAvante; receives royalties from American Psychiatric Publishing, Inc, Guilford Publications, Herald House, and WW Norton & Company; has provided expert testimony for Jones Day (Wyeth litigation), Philips Lyttle, LLP (GlaxoSmithKline litigation), and Pepper Hamilton, LLP (Lilly litigation); has received research funding (during the past 3 years) from Eli Lilly, Forest, GlaxoSmithKline, Sepracor, and the National Institute of Mental Health (NIMH); and his spouse is an employee of Advogent, which does business with Bristol-Myers Squibb and Wyeth.* ***Dr Gaynes*** *is a consultant for Bristol-Myers Squibb and has received grant/research support from NIMH, the Agency for Healthcare Research and Quality, M3 Corporation, Bristol-Myers Squibb, and Novartis.* ***Dr Papakostas*** *is a consultant for GlaxoSmithKline, Eli Lilly, Shire, Otsuka, Pierre Fabre, and PamLab; has received grant/research support from NIMH, Pfizer, Forest, Precision Human Biolaboratories, and Bristol-Myers Squibb; has received honoraria from GlaxoSmithKline, Eli Lilly, Shire, Otsuka, Pierre Fabre, Bristol-Myers Squibb, Pfizer, PamLab, and Lundbeck; and is on the speakers/advisory board for Bristol-Myers Squibb.* ***Dr Shelton*** *has received grant/research support from Eli Lilly, GlaxoSmithKline, Janssen, Pfizer, Sanofi-Aventis, Merck, Forest, Gideon-Richter, Wyeth, AstraZeneca, Abbott, Novartis AG, Otsuka America, and PamLab and is a paid consultant for Pfizer, Janssen, Forest, Gideon-Richter, Merck, and Sierra.* ***Dr Trivedi*** *has received research support from Bristol-Myers Squibb, Cephalon, Corcept, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Merck, NIMH, the National Alliance for Research in Schizophrenia and Depression, Novartis, Pfizer, Pharmacia & Upjohn, Predix, Solvay, and Wyeth-Ayerst; is an advisor/consultant for Abbott, Akzo (Organon), AstraZeneca, Bayer, Bristol-Myers Squibb, Cephalon, Cyberonics, Fabre-Kramer, Forest, GlaxoSmithKline, Janssen, Johnson & Johnson, Eli Lilly, Meade Johnson, Neuronetics, Parke-Davis, Pfizer, Pharmacia & Upjohn, Sepracor, Solvay, VantagePoint, and Wyeth-Ayerst; and is a member of the speakers/advisory boards for Abdi Brahim, Akzo (Organon), Bristol-Myers Squibb, Cephalon, Cyberonics, Forest, GlaxoSmithKline, Janssen, Eli Lilly, Pharmacia & Upjohn, Solvay, and Wyeth-Ayerst.*

The opinions expressed herein are those of the faculty and do not necessarily reflect the views of the CME provider and publisher or the commercial supporter.

doi:10.4088/PCC.8133ah3c

Overview of Partial Response and Nonremission in Depression

Prevalence

Michael E. Thase, MD, defined the clinical remission of a depressive episode as a complete relief of the signs and symptoms of the presenting episode.[1] The individual should also return to his or her normal level of social and functional capacity.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study of 2,876 patients found that nearly 80% of patients had chronic or recurrent depression.[2] Only 33% achieved a level of symptom resolution by the end of the acute phase of treatment that would place them within the remission range according to scores on the Quick Inventory of Depressive Symptomatology (QIDS). Approximately 14% improved but had too many symptoms to be considered remitted. About 53% of patients did not improve or improved only minimally.

Consequences

Dr Thase noted that remission has become the gold standard for depression treatment because patients who do not remit have a poorer prognosis than those who do achieve remission. Patients who have not fully remitted are at a greater risk of relapse and recurrence, have more chronic depressive episodes and psychiatric and medical comorbidities, and experience greater impairment in work and relationships than patients who achieved remission.[3] Sustained depression may also increase the lifetime risk of suicide.[4]

Risk Factors

Risk factors for incomplete remission, said Dr Thase, include high severity, comorbidity, chronicity, and lack of social support in combination with high stress. These risk factors affect the complexity of the clinical situation. The more complex the patient's situation, the greater the likelihood that a longer period of treatment will be necessary to achieve full remission, and the greater the likelihood that the individual, even if he or she has responded to treatment, will have too high a level of residual symptoms to be declared fully remitted.

Tracking Outcomes

According to Dr Thase, one of the most important ways in which physicians can help their patients achieve remission is by carefully tracking symptoms. Patients may start feeling better after beginning a treatment regimen and might overemphasize their level of improvement at a clinical visit because they have not felt well for so long. Relying on the global statement "I'm definitely better" from the patient overlooks persistent, minor, or residual symptoms. Dr Thase recommended using a standardized symptom assessment measure and keeping track of the patient's levels of symptom burden.

After an outcomes measure has been established, the clinician should optimize each treatment trial for the patient. If the current treatment is well tolerated and the individual has made significant symptom improvement but is still experiencing residual symptoms, then it may be necessary to adjust the treatment dose, add another medication, or combine pharmacotherapy and psychotherapy. Dr Thase encouraged physicians to make sure that each treatment trial has the best chance of working for a patient.

FOR CLINICAL USE

- Monitor patients for incomplete remission.
- Identify clinical subtypes and medical or psychiatric comorbidities that increase the risk of treatment-resistant depression.
- Ensure that patients are complying with their treatment regimen and consider the potential loss of partial benefit from the first-line treatment before augmenting, combining, or switching medications.
- Use measurement-based tools for assessing symptoms, adverse events, and patient adherence.

Also important is identifying comorbid conditions and treating those conditions specifically. However, if the comorbidities have been managed and the initial treatment trial has been optimized, but the clinician has been measuring symptoms and finds that the patient has an incomplete remission, interventions must be made.

Conclusion

Incomplete remission is a common and suboptimal outcome of acute phase treatment of depression. Incomplete remission is more likely to occur among patients with complex presentations, such as comorbidities, severe episodes, or lack of social support. Dr Thase recommended that clinicians adopt the habit of monitoring the ongoing level of a patient's symptomatic status as the best way to determine if the response should be characterized as remission or as a partial response.

Identifying Difficult-to-Treat Depression and Differential Diagnosis

Bradley Gaynes, MD, explained that difficult-to-treat depression, or treatment-resistant depression, has no single accepted definition. One definition is the failure to reduce depressive severity by at least 50% following treatment. Another is a failure to reduce absolute depression scale scores below a specific remission threshold. It may also mean a failure of symptoms to entirely remit or to respond to one or more prior antidepressant trials.

However, many patients who are considered treatment resistant are either misdiagnosed or inadequately treated. Accurate diagnosis of treatment-resistant depression requires examining both primary and comorbid causes of the depression.

While no consensus definition exists, Dr Gaynes offered a basic definition of *treatment-resistant depression*: an inadequate response to at least 2 antidepressant trials that were adequate in dose, duration, and treatment adherence. While some experts suggest that the trials should involve 2 different pharmacologic classes, the STAR*D data[5] do not support this distinction.

Maintaining Remission as the Goal

Dr Gaynes stated that the fewer treatment steps needed to attain remission, the higher the remission rates. In STAR*D,[6] approximately one-third of patients remitted after an initial antidepressant treatment. For those who failed this first treatment, the next treatment led to remission in about 31%. Following that, however, the likelihood of remission dropped off substantially, to about 14% and 13% in the third and the fourth trials, respectively. However, because remission is associated with a better prognosis, even if several treatments are needed to bring about remission, the objective is to keep striving toward remission.

Distinguishing Resistance From Misdiagnosis

When treating those who are resistant to treatment, the clinician should first determine whether the primary diagnosis is correct. For example, the patient's mood syndrome may be prompted by a primary substance use disorder, or the patient may have a primary medical condition such as hypothyroidism that is not being treated.

Unrecognized psychotic depression or bipolar depression can also explain partial response, and treating these disorders with only antidepressants is likely to worsen the course of illness. Dr Gaynes added that bipolar depression is more prevalent than bipolar mania,[7] and the depressive presentation within bipolar disorder is often difficult to distinguish from a major depressive episode. Dr Gaynes recommended obtaining a patient history and corroborating information from individuals close to the patient to identify whether a major depressive episode might be part of a bipolar diagnosis.

Recognizing Risk Factors

Clinicians should identify clinically relevant risk factors for difficult-to-treat depression, said Dr Gaynes, so that these patients can receive more aggressive monitoring and treatment.

Chronicity. Chronic depression is a subtype of depression in which a current major depressive episode lasts 2 years or longer or does not fully resolve between episodes.[8] Chronic depression substantially increases the likelihood of treatment-resistant depression and also increases the time necessary to achieve response or remission.

Dysthymia commonly co-occurs with major depressive disorder (MDD). In this instance, known as double depression, an individual has an underlying dysthymic disorder—a chronic, low-grade but impairing depressive illness—and superimposed upon this state are episodes of major depression.

This combination puts patients at high risk of difficult-to-treat depression.[9]

Severity. The greater the severity of a depressive episode, the more likely the patient is to present with treatment-resistant depression. Greater depressive severity is also associated with greater functional impairment, a greater risk of a subsequent recurrence of a major depressive episode, and a greater likelihood of suicide attempts compared with an episode mild or moderate in severity.[8]

Comorbidities. Psychiatric comorbidities, including anxiety disorders, increase the likelihood of difficult-to-treat depression.[10] Anxiety disorders increase the chance of patients having more severe depressive symptoms, suicide attempts, decreased responsiveness to treatment, and a greater susceptibility to side effects.[8] Substance use disorders and personality disorders are also indicators of difficult-to-treat depression and may require multiple treatment modalities.

Dr Gaynes explained that comorbid clusters of subsyndromal symptoms may also increase the risk of difficult-to-treat depression.[10] The presence of these symptom clusters, such as anxiety features that do not meet criteria for a separate diagnosis, decreases the likelihood of a patient achieving remission.

Comorbid medical conditions, such as diabetes, cardiac disease, and pain, may also increase the likelihood of a difficult-to-treat depression.[8] Concurrent medications for medical disorders may also have side effects that exacerbate a depressive disorder.

Patient and Physician Factors

Patient and physician factors may contribute to incomplete remission. Patient factors may involve compliance issues or unusual pharmacokinetics. An individual who has a unique metabolism may require a much higher dose of a medication than someone with a normal metabolism. Differences in pharmacokinetics can also affect tolerability of medications.

Physicians may inadvertently contribute to difficult-to-treat depression by not allowing for a full, adequate trial of antidepressant treatment in terms of dose or duration.

Conclusion

Dr Gaynes concluded that incomplete remission requires aggressive identification and management. Key diagnostic considerations include ensuring that the primary diagnosis is correct, identifying clinical subtypes that increase the risk of difficult-to-treat depression, and recognizing and treating comorbid medical or psychiatric comorbidities. Physicians must also verify that an individual receives an adequate dose and duration of treatment and adheres to the treatment plan.

Measurement-Based Assessments for Difficult-to-Treat Depression

The major focus during the initial treatment phase, said Madhukar H. Trivedi, MD, should be to achieve sustained remission of depression through a systematic approach of measuring symptoms, side effects and adverse events, patient adherence, and safety in terms of suicidality and other risk factors.

Two large practical clinical trials, the Texas Medication Algorithm Project (TMAP)[11] and STAR*D,[6] took a measurement-based approach in which a rating scale was used in every treatment interaction, either by the patient or by the clinician. Measurement-based care helps ensure vigorous dosing and movement toward remission.

Assessment Tools for Depression

Dr Trivedi listed rating scales commonly used to assess depression (Table 1).[12–17] Of those, the QIDS,[17] the Patient Health Questionnaire (PHQ-9),[16] and the Beck Depression Inventory (BDI)[12] are practical scales that allow for the ongoing monitoring of patients in the clinical setting.

Measurement-Based Care

For treatment programs for depressed patients, Dr Trivedi recommended that the clinician select a first-line treatment based on patient participation, assume the need for a sequence or combination of treatments if the first one is not successful, and make treatment decisions appropriately based on the measurement domains. The clinician needs to know what symptoms to monitor and how to monitor those symptoms to assess progress and possibly modify treatment.

According to Dr Trivedi, measurement-based care means collecting information at critical decision points in the course of treatment to decide when to declare treatment failure, what to do with partial improvement, and how long to continue successful treatment or discontinue.

Tactics to Optimize Treatment

Dr Trivedi reviewed examples of how measurement tools can be used in practice to optimize treatment.

Adherence. Patients complete a self-report Patient Medication Adherence Questionnaire (PMAQ) at each visit or contact. Patients are often unwilling or unable to tell the clinician about nonadherence, but they are much more comfortable giving that information in a self-report.

Patients who missed ≥ 3 of the previous 14 days of medication should be considered nonadherent. If nonadherence was due to side effect concerns, then those side effects can be addressed. If adherence is low for reasons other than side effects, the physician can consider continuing the current treatment and dose.

Side effects. Dr Trivedi advised clinicians to use the Frequency, Intensity,

Table 1. Commonly Used Rating Scales for Assessing Depression

Scale	Purpose	Patient- or Clinician-Rated
Beck Depression Inventory (BDI)[12]	Identify a likely cause of depression and assess symptom severity[a]	Patient
Frequency, Intensity, and Burden of Side Effect Rating (FIBSER)[13]	Track medication side effects	Patient
Hamilton Depression Rating Scale (HDRS)[14]	Assess depression symptoms severity and track changes in symptoms	Clinician
Montgomery-Åsberg Depression Rating Scale (MADRS)[15]	Identify a likely cause of depression and assess symptom severity[a]	Clinician
Patient Health Questionnaire (PHQ-9)[16]	Identify a likely cause of depression and track change symptoms[a]	Patient
Patient Medication Adherence Questionnaire (PMAQ)	Monitor medication adherence	Patient
Quick Inventory of Depression Symptomology (QIDS)[17]	Identify a likely cause of depression[a]	Both

[a]Likely causes of depression would subsequently need clinical confirmation.

and Burden of Side Effect Rating Scale (FIBSER).[13] A FIBSER score of 5 to 6 on the burden item indicates that patients are experiencing intolerable side effects and that treatment alternatives should be considered.

For patients whose side effects are unacceptable, tactics include decreasing the dose, managing the side effects directly and continuing the medication regimen, or switching medication. For patients whose side effects are tolerable, tactics include decreasing the dosage or continuing the medication at the same dose but managing the side effects.

Symptoms. The QIDS-SR and the PHQ-9 are effective tools for measuring symptoms. Patients not responding to medication, on the basis of PHQ-9 scores ≥ 9, should have their medication or medications increased until maximum doses are reached, assuming side effects are not problematic. Patients with PHQ-9 scores ranging from 5 to 8 should have their medication increased or maintained at the same dosage starting at week 4, assuming side effects are not problematic. Patients with a PHQ-9 score < 5 may be maintained at the same dosage starting at week 4, again assuming side effects are not problematic.

Assessment frequency. Dr Trivedi stated that, in accordance with the American Psychiatric Association Guidelines,[18] patients should be assessed at least every 2 weeks for the first 6 weeks of each treatment step, or as often as possible. Telephone follow-up visits can be done at the clinician's discretion. Then, clinicians can see patients every 3 weeks until the patient experiences remission or adequate response or until a change in treatment strategy is made. Once remission is achieved, the clinician should assess the patient every 3 months.

Conclusion

Dr Trivedi concluded that the best approach to achieving the goal of sustained remission is to use a systematic assessment method, with the use of measurement tools for symptoms, adverse events, and patient adherence, to inform clinical decision points.

Switching, Augmentation, and Combination Strategies for Partial Responders

While many antidepressants are available for the treatment of MDD, George I. Papakostas, MD, explained, they have limitations in efficacy, safety, and tolerability. According to a meta-analysis[19] of randomized, double-blind, placebo-controlled studies from 1980 to 2008, the absolute efficacy for antidepressants is about 50% in terms of response rates, with a relative efficacy versus placebo of about 15%.

Dr Papakostas noted that, even among antidepressant remitters, many patients may continue to experience residual symptoms, including sleep disturbance, fatigue, diminished interest or pleasure, guilt, and poor concentration.[20]

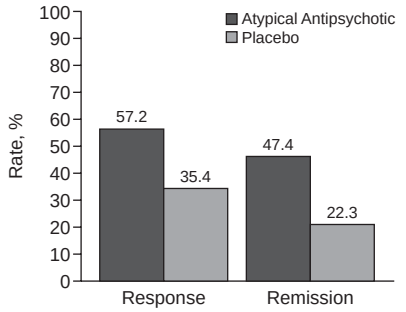
Treatment Approaches

Dr Papakostas named 4 broad pharmacologic approaches for the management of patients with insufficient symptom response: (1) increase the dose of the antidepressant, (2) switch from one antidepressant to another, (3) add a nonantidepressant agent to the antidepressant treatment regimen (augmentation), and (4) add a second antidepressant to the antidepressant regimen (combination).

Augmentation and combination (polypharmacy) strategies have some advantages over dose increase and switching (monotherapy) strategies. Polypharmacologic strategies avoid the loss of any therapeutic benefit from the first-line agent as well as the risk of withdrawal symptoms that may occur upon switching. Further, the augmenting agent may be chosen not only to resolve the depression but also to target side effects of the first-line therapy.

Disadvantages to polypharmacy include compliance problems, a greater risk of drug interactions, the persis-

Figure 1. Pooled Response and Remission Rates in Treatment-Resistant Depression[a]



[a]Reprinted with permission from Papakostas et al.[21]

tence and compounding of side effects, and the cost of multiple medications. Usually, fewer drugs means less cost, but the selection of generic versus branded medications does influence this factor.

Augmentation and Combination Strategies

Atypical antipsychotics. The most comprehensively studied treatment strategy for resistant depression or for inadequate response to antidepressants is augmentation with atypical antipsychotic agents. A meta-analysis[21] of randomized, double-blind, placebo-controlled studies found that augmentation of various antidepressants with the atypical antipsychotic agents olanzapine, risperidone, and quetiapine was more efficacious than adjunctive placebo therapy (Figure 1). In addition, Dr Papakostas noted that the atypical antipsychotic aripiprazole was recently approved by the US Food and Drug Administration (FDA) for use as an adjunctive therapy to antidepressants in MDD.

Augmenting with atypical antipsychotics has so far been the best studied strategy for managing treatment-resistant depression, said Dr Papakostas. However, the disadvantage is that, depending on the agent that is chosen, atypical antipsychotics are associated with various side effects, including neuroendocrine side effects (ie, hyperprolactinemia), metabolic side effects (ie, weight gain, glucose dysregulation, hyperlipidemia), and extrapyramidal side effects (ie, akathisia, parkinsonism, dyskinesia, neuroleptic malignant syndrome, tardive dyskinesia).

Table 2. Evidence-Based Relative Efficacy of Augmentation and Combination Agents in Treatment-Resistant Depression[a]

Strategy	Grade[b]
Augmentation/Combination	
Atypical antipsychotics[21,22]	A
Mirtazapine/mianserin[23,24]	A–
Omega-3 fatty acids[25]	A–
Modafinil,[28] lithium,[29] T_3[30]	B
Bupropion[32]	B
Testosterone,[26] mecamylamine,[27] desipramine[31]	B–
Pindolol,[33] buspirone,[34] inositol[35]	C
Lamotrigine,[36] methylphenidate[37]	C
Switching	
SSRI to SNRI, NDRI, or SNRA[38]	A
SSRI to SSRI[38]	A
Switching to MAOI[39,40]	B
Switching to TCA[39]	C

[a]The efficacy grades were derived by Dr Papakostas from reviewing all randomized, double-blind, placebo-controlled studies for these compounds in addition to data from STAR*D, which was not placebo-controlled. The grading criteria specifically focused on the number of studies that demonstrated superiority versus equivalence of each of the treatment strategies.
[b]A = good efficacy data, B = mixed efficacy data, C = weak efficacy data.
Abbreviations: MAOI = monoamine oxidase inhibitor, NDRI = norepinephrine-dopamine reuptake inhibitor, SNRA = serotonin-norepinephrine receptor antagonist, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, T_3 = triiodothyronine.

Other strategies. Dr Papakostas went on to discuss a number of other strategies (Table 2).[21–40] Of those, he stated that, following augmentation of antidepressants with atypicals, the second best-studied augmentation strategy is the addition of lithium to tricyclic antidepressants for patients with MDD who demonstrate inadequate response to tricyclic therapy. He cautioned that each strategy has its advantages and disadvantages.

Augmentation and combination in STAR*D. The goal of the STAR*D study[41] was to assess the relative efficacy, safety, and tolerability of different treatment strategies for antidepressant-resistant MDD. The study design involved 4 levels. The first level was an open-label trial of the SSRI citalopram for acute MDD, and each successive level involved different augmentation, combination, or switching strategies. Patients advanced from one level to the next if they did not demonstrate adequate depressive symptom response.

The use of various augmentation and combination strategies within the STAR*D study was examined in Levels 2 and 3. Level 2 focused on the addition of the bupropion or buspirone.[42] Remission rates were similar to those in Level 1, but a statistically significant advantage in terms of tolerability was found favoring bupropion combination ($P < .05$).

Level 3 examined adjunctive lithium versus T_3 for depressed patients who failed 2 adequate antidepressant trials. The results of this study[43] demonstrated a large numerical but not statistically significant advantage in remission rates in favor of T_3 versus lithium augmentation, as well as a significant advantage in favor of T_3 augmentation over lithium augmentation in tolerability ($P < .05$).

Switching Medication

Dr Papakostas and colleagues[38] recently conducted a meta-analysis to examine differences in efficacy between switching to a second SSRI versus switching to a newer, non-SSRI antidepressant (venlafaxine, bupropion, or mirtazapine) for SSRI-resistant depression. Switching to a non-SSRI agent had a small numerical but statistically significant ($P < .05$) advantage for remission over switching to a second SSRI. Switching to a second SSRI, however, was better tolerated.

Switching between a TCA (imipramine) and an MAOI (phenelzine) has been studied as well, noted Dr Papakostas. While switching in either direction produced more response than the initial agent, switching to phenelzine for imipramine-resistant depression was superior to switching to imipramine in phenelzine-resistant depression.[39] Another study[44] found that switching to the SSRI sertraline for imipramine-resistant depression and switching to imipramine for sertraline-resistant depression were both efficacious, although the switch to sertraline produced a higher response rate.

Switching in STAR*D. In Level 2 of STAR*D, patients could switch from citalopram to sertraline, venlafaxine, or bupropion.[41] Remission rates were similar among the groups, about 25%.[5]

In Level 3 of STAR*D, switch options were mirtazapine or nortriptyline. Remission rates did not differ statistically, but both were modest (< 20%).[45]

Finally, in Level 4 of STAR*D, switching to the MAOI tranylcypromine had no advantage over switching to the combination of mirtazapine and venlafaxine, and remission rates were again modest (< 15%). However, the combination of mirtazapine and venlafaxine was better tolerated than tranylcypromine.[40]

Conclusion

When choosing whether to pursue augmentation or combination versus a monotherapy strategy, such as increasing the dose or switching, clinicians should consider not only the potential loss of partial benefit from the first-line treatment trial as well as the risk of withdrawal symptoms, but also the tolerability of the first-line treatment trial and the risk of drug interactions.

Long-Term Management Strategies for Depression

The management of depressive relapse and recurrence requires an active stance on the part of the treating clinician from the beginning of treatment; the physician should try to change fundamental risk factors for the return of depressive symptoms, began Richard C. Shelton, MD. Instead of being reactive to problems that the patient may develop going forward, the clinician should anticipate those problems.

One of the basic findings from the STAR*D study was that depression is much tougher to treat than originally thought. Patients treated using an algorithmic format had a hard time getting to complete remission.[46] The majority of changes that occurred in patients happened at the first step, and the proportional change in depression symptoms decreased substantially over the course of the study.[6] Thus, said Dr Shelton, the long-term management of depression should be viewed in the context of acute treatment and the need for early aggressive management to get the patient as well as possible.

Predicting and Preventing Relapse

Dr Shelton recommended that the clinician think about risk factors for subsequent relapse before treatment is even started. Specific modifiable issues in a patient's life that contribute to depressive episodes need to be actively managed, such as stressful events like family problems as well as risk factors for cerebrovascular disease and subsequent vascular depression.

Addressing and managing causal or prodromal factors for subsequent depressive events as early as possible may prevent a full relapse. For example, a patient who has been in treatment for a year to 2 years may suddenly have difficulty with sleeping or anxiety or may be experiencing a loss of interest or motivation. Even in later stages of treatment, these adverse events can increase the patient's risk of relapse, explained Dr Shelton.

Nonpharmacologic Therapies for Depression

Dr Shelton cited 2 studies[47,48] that compared the efficacy of antidepressant medication to that of cognitive therapy in patients with moderate to severe depression. Depending on the expertise of the therapist, cognitive therapy can provide similar efficacy to antidepressant medication during acute treatment.[47] At the 2-year follow-up after 1 year of no treatment,[48] patients who had previously received cognitive therapy had a significantly lower rate of relapse (31%) than patients who had discontinued medication treatment (76%; $P = .004$) and a similar rate as those who continued antidepressant treatment (47%, $P = .20$). These results suggest that cognitive therapy has a different effect in the treatment of depression than antidepressants; this effect appears to modify the risk for relapse.

Mechanisms of Treatment Response

When antidepressant treatment is applied, response mechanisms may reduce symptoms by directly affecting the structures in the brain that are generating symptoms. However, explained Dr Shelton, treatments may need to target potential causal mechanisms or vulnerability factors to reduce relapse and recurrence. There is still a question whether cognitive therapy and medications (if effective) change depressive symptoms, and then, as a result, fundamental cognitive processes are changed, or treatment produces symptom response indirectly by directly changing the fundamental cognitive processes.

Evidence suggests that medications, particularly SSRIs, produce symptomatic change through direct, physiologic inhibition of the activity of the brain region thought to underlie anxiety and depressive symptoms.[49] However, cognitive therapy may mediate the psychological factors that predispose

someone to depressive episodes in a way that antidepressant medicines do not.[50] These predisposing factors include hopelessness, dysfunctional attitude, and attributional style.

Thus, Dr Shelton said, whereas antidepressant medications appear to produce a direct effect on brain structures that mediate the symptoms, cognitive therapy appears to act more indirectly through underlying psychological processes that modify risk for depression, so that the risk for relapse is decreased.

Long-Term Management of MDD

When considering long-term management of patients with depression, clinicians should focus on modifiable risk factors for relapse or recurrence at all phases of treatment, recommended Dr Shelton. Many patients may do well with pharmacologic treatment and become essentially asymptomatic, but most patients will not fully remit with any single treatment. Therefore, Dr Shelton suggested focusing on change in cognitive mediators of relapse and recurrence that are likely to be changed through either cognitive therapy or behavioral activation.

Dr Shelton also recommended actively managing comorbidity, residual depressive symptoms, and predictable stressors. Unfortunately, clinicians often focus on symptom remission without identifying the psychosocial factors that may increase risk for return of symptoms.

Therapeutic Candor in Practice

According to Dr Shelton, therapeutic candor means avoiding "overselling" treatment. He recommends avoiding the "silver bullet" concept with regard to acute treatment and managing patients' expectations. Most patients are eventually going to have a significant return of depressive symptoms that will typically occur within the first 12 months after initial response to treatment. Therefore, the management of expectations in the acute phase means helping people to understand the importance of relapse prevention.

Patients also need to understand that residual symptoms are the rule, not the exception. Dr Shelton noted that it is common for people to continue to have significant symptoms, and patients have a responsibility to modify risk factors for becoming depressed again.

Often, after the first few weeks of treatment, clinicians may become less aggressive and less systematic over the course of treatment. Dr Shelton advised clinicians to be aggressive in treatment and stay active over time, asking themselves if everything has honestly been done to help the patient. Clinicians must decide if further change is realistic. For example, if a patient is taking medication, how much change is realistic on that treatment regimen? Should the clinician involve the patient in cognitive therapy?

Finally, physicians need to be honest about their time commitments and engage alternative providers when useful. Many patients will benefit from more regular contact with someone like a case manager or a therapist. Ongoing support for those patients may be needed in order to be able to provide optimal long-term treatment.

Drug names: aripiprazole (Abilify), bupropion (Aplenzin, Wellbutrin, and others), buspirone (BuSpar and others), citalopram (Celexa and others), desipramine (Norpramin and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), mecamylamine (Inversine), methylphenidate (Metadate, Ritalin, and others), mirtazapine (Remeron and others), modafinil (Provigil), nortriptyline (Pamelor and others), olanzapine (Zyprexa), phenelzine (Nardil), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), tranylcypromine (Parnate and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, buspirone, lithium, mecamylamine, methylphenidate, modafinil, quetiapine, risperidone, inositol, pindolol, and triiodothyronine are not approved by the US Food and Drug Administration for the treatment of major depressive disorder; lamotrigine is not approved for the treatment of major depressive disorder or for acute phase therapy of bipolar depression; olanzapine is not approved for major depressive disorder except in combination with fluoxetine; and mianserin is not approved for use in the United States.

REFERENCES

1. Thase ME. Introduction: defining remission in patients treated with antidepressants. *J Clin Psychiatry.* 1999;60 (suppl 22):3–6.
2. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry.* 2006;163(1): 28–40.
3. McIntyre RS, O'Donovan C. The human cost of not achieving full remission in depression. *Can J Psychiatry.* 2004;49 (3, suppl 1):10S–16S.
4. Judd LL, Akiskal HS, Paulus MP. The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. *J Affect Disord.* 1997;45(1–2):5–18.
5. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion SR, sertraline, or venlafaxine XR after failure of SSRIs for depression. *N Engl J Med.* 2006;354(12):1231–1242.
6. Rush AJ, Trivedi JH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* 2006;163(11):1905–1917.
7. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry. 2002;59(6):530–537.
8. Kornstein SG, Schneider RK. Clinical features of treatment-resistant depression. *J Clin Psychiatry.* 2001;62(suppl 16): 18–25.
9. McCullough JP Jr, Klein DN, Keller MB, et al. Comparison of DSM-III-R chronic major depression and major depression superimposed on dysthymia (double depression): validity of the distinction. *J Abnorm Psychol.* 2000;109(3):419–427.
10. Rush AJ, Wisniewski SR, Warden D, et al. Selecting among second-step antidepressant medication monotherapies: predictive value of clinical, demographic, or first-step treatment features. *Arch Gen Psychiatry.* 2008;65(8):870–880.
11. Trivedi MH, Rush AJ, Crismon ML, et al. Clinical results for patients with major depressive disorder in the Texas Medication Algorithm Project. *Arch Gen Psychiatry.* 2004;61(7):669–680.
12. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961;4:561–571.
13. Wisniewski SR, Rush AJ, Balasubramani GK, et al. Self-rated global measure of the frequency, intensity, and burden of side effects. *J Psychiatr Pract.* 2006;12(2): 71–79.
14. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23:56–62.
15. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134: 382–389.
16. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9): 606–613.
17. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-item Quick Inventory of Depressive Symp-

tomatology (QIDS), Clinician Rating (QIDS-C), and Self-Report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry.* 2003;54(5):573–583.
18. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder. 2nd edition. Available at: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=MDD2e_05-15-06. Accessed May 20, 2009.
19. Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome? a meta-regression of double-blind, randomized clinical trials in MDD. *Eur Neuropsychopharmacol.* 2009;19(1):34–40.
20. Nierenberg AA, Keefe BR, Leslie VC, et al. Residual symptoms in depressed patients who respond acutely to fluoxetine. *J Clin Psychiatry.* 1999;60(4):221–225.
21. Papakostas GI, Shelton RC, Smith J, et al. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. *J Clin Psychiatry.* 2007;68(6):826–831.
22. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2007;68(6):843–853.
23. Holm KJ, Markham A. Mirtazapine: a review of its use in major depression. *Drugs.* 1999;57(4):607–631.
24. Aizenberg D, Gur S, Zemishlany Z, et al. Mianserine, a 5-HT2a/2c and alpha 2 antagonist, in the treatment of sexual dysfunction induced by serotonin reuptake inhibitors. *Clin Neuropharmacol.* 1997;20(3):210–214.
25. Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry.* 2002;159(3):477–479.
26. Pope HG, Cohane GH, Kanayama G, et al. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *Am J Psychiatry.* 2003;160(1):105–111.
27. George TP, Sacco KA, Vessicchio JC, et al. Nicotinic antagonistic augmentation of selective serotonin reuptake inhibitor-refractory major depressive disorder: a preliminary study. *J Clin Psychopharmacol.* 2008;28(3):340–344.
28. Fava M, Thase ME, DeBattista C, et al. Modafinil augmentation of selective serotonin reuptake inhibitor therapy in MDD partial responders with persistent fatigue and sleepiness. *Ann Clin Psychiatry.* 2007;19(3):153–159.
29. Bauer M, Dopfmer S. Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *J Clin Psychopharmacol.* 1999;19(5):427–434.
30. Aronson R, Offman HJ, Joffe RT, et al. Triiodothyronine augmentation in the treatment of refractory depression: a meta-analysis. *Arch Gen Psychiatry.* 1996;53(9):842–848.
31. Nelson J, Mazure C, Jatlow P, et al. Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. *Biol Psychiatry.* 2004;55(3):296–300.
32. Zisook S, Rush AJ, Haight BR, et al. Use of bupropion in combination with serotonin reuptake inhibitors. *Biol Psychiatry.* 2006;59(3):203–210.
33. Maes M, Vandoolaeghe E, Desynder R. Efficacy of treatment with trazodone in combination with pindolol or fluoxetine in major depression. *J Affect Disord.* 1996;41(3):201–210.
34. Appelberg BG, Syvälahti EK, Koshinen TE, et al. Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in. *J Clin Psychiatry.* 2001;62(6):448–452.
35. Nemets B, Mishory A, Levine J, et al. Inositol addition does not improve depression in SSRI treatment failure. *J Neural Transm.* 1999;106(7–8):795–798.
36. Barbosa L, Berk M, Vorster M. A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated fluoxetine for resistant major depressive episodes. *J Clin Psychiatry.* 2003;64(4):403–407.
37. Ravindran AV, Kennedy SH, O'Donovan MC, et al. Osmotic-release oral system methylphenidate augmentation of antidepressant monotherapy in major depressive disorder: results of a double-blind, randomized, placebo-controlled trial. *J Clin Psychiatry.* 2008;69(1):87–94.
38. Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. *Biol Psychiatry.* 2008;63(7):699–704.
39. McGrath PJ, Stewart JW, Nunes EV, et al. A double-blind crossover trial of imipramine and phenelzine for outpatients with treatment-refractory depression. *Am J Psychiatry.* 1993;150(1):118–123.
40. McGrath PJ, Stewart JW, Fava M, et al. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. *Am J Psychiatry.* 2006;163(9):1531–1541.
41. Rush AJ, Trivedi M, Fava M. Depression, IV: STAR*D treatment trial for depression. *Am J Psychiatry.* 2003;160(2):237.
42. Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med.* 2006;354(12):1243–1252.
43. Nierenberg AA, Fava M, Trivedi MH, et al. A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR*D report. *Am J Psychiatry.* 2006;163(9):1519–1530.
44. Thase ME, Rush AJ, Kornstein SG, et al. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. *Arch Gen Psychiatry.* 2002;59(3):233–239.
45. Fava M, Rush AJ, Wisniewski SR, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. *Am J Psychiatry.* 2006;163(7):1161–1172.
46. Trivedi MH, Daly EJ. Treatment strategies to improve and sustain remission in major depressive disorder. *Dialogues Clin Neurosci.* 2008;10(4):377–384.
47. DeRubeis RJ, Hollon SD, Amsterdam JD, et al. Cognitive therapy vs medications in the treatment of moderate to severe depression. *Arch Gen Psychiatry.* 2005;62(4):409–416.
48. Hollon SD, DeRubeis RJ, Shelton RC, et al. Prevention of relapse following cognitive therapy vs medications in moderate to severe depression. *Arch Gen Psychiatry.* 2005;62(4):417–422.
49. Sheline YI, Barch DM, Donnelly JM, et al. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an FMRI study. *Biol Psychiatry.* 2001;50(9):651–658.
50. DeRubeis RJ, Evans MD, Hollon SD, et al. How does cognitive therapy work? Cognitive change and symptom change in cognitive therapy and pharmacotherapy for depression. *J Consult Clin Psychol.* 1990;58(6):862–869.

For the CME Posttest for this ACADEMIC HIGHLIGHTS, see pages 178–179.