MD CONFERENCE EXPRESS

Options for Treatment-Resistant Depression

Written by Maria Vinall

Only about 50% of patients with major depressive disorder will respond after their first treatment, and of these responders, only 50% to 70% will achieve symptom remission [Rush AJ et al. *Am J Psychiatry* 2003]. Linda Carpenter, MD, Brown University, Providence, RI, discussed several pharmacological strategies (see sidebar) that are used in patients whose depression is resistant to treatment (TRD) after optimized monotherapy has been attempted.

Switching medications has been shown to have several benefits for these individuals, including a lower risk of drug-drug interactions, and an improved response that is associated with either a different mechanism of action or a different side effect profile. A switch strategy (versus a combination or augmentation strategy) also makes it easier to know what is working and is usually less expensive than multiple agents. A potential disadvantage of switching is the risk of losing any partial benefits that may have been achieved with the first drug.

A common question when considering a switch strategy is whether it is necessary to switch drug class. Although some studies indicate relatively high response rates with another SSRI after the first SSRI failure [Calabrese JR et al. *J Clin Psychiatry* 2003; Thase ME et al. *Depress Anxiety* 2002 & *J Clin Psychiatry* 2001], a recently published meta-analysis suggests a modest risk benefit in favor of switching classes after the first SSRI failure [Papakostas GI et al. *Dialogues Clin Neurosci* 2008].

A combination strategy may be beneficial when the 2 medications have different mechanisms of action that work in synergy. At least 1 study that compared combining an SSRI with a tricyclic showed that the combination was significantly (p=0.001) more likely to result in remission than either drug alone [Nelson JC et al. *Biol Psychiatry* 2004].

Augmentation with a second agent that is not an antidepressant is a widely practiced strategy. In the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial, augmenting citalopram with either bupropion SR or buspirone produced similar rates of remission (30%), but greater symptom reduction and better tolerance were seen with bupropion SR [Trivedi MH et al. *N Engl J Med* 2006]. There is also growing evidence for augmentation with atypical antipsychotics, including the results of a meta-analysis [Nelson JC & Papakostas GI in review] that indicates favorable outcomes with the atypicals as a class compared with placebo. Other drugs that have been studied as adjunct therapy include tri-iodothyronine, lithium, modafinil, stimulants, and eszopiclone.

"There are many reasonable next steps after a first drug failure, and there is nothing to indicate that any one is the best or worst choice. It may be that side effect profiles will determine the choice of treatment," said Dr. Carpenter.

While electroconvulsive therapy (ECT) can be very effective for some patients who do not respond to pharmacological treatment for their depression, it has a poor side effect profile and a high relapse rate (~50% in 6 months). Further, another 20% of patients do not remit even after ECT. William M. McDonald, MD, Emory University Medical School, Atlanta, GA, discussed several of the somatic treatments that are emerging as options for these patients.

Vagus nerve stimulation (VNS) is an adjunctive therapy for TRD that uses an implanted stimulator to send electric impulses to the left vagus nerve in the neck via a lead wire that is implanted under the skin. It is only approved for patients who have not responded to 4 different antidepressant treatments. Key questions with VNS are determining who is likely to respond (eg, Do ECT failures respond?) and whether VNS might be an alternative for

Highlights from the
American Psychiatric Association 2009 Annual Meeting

maintenance ECT. Although trials are ongoing, in the United States the treatment has been defunded and appears to be declining.

Transcranial magnetic stimulation (TMS) is noninvasive technique that uses a magnetic field to induce a small electric current in a specific part of the brain without causing seizure or loss of consciousness. Results of a large clinical trial showed response and remission rates with active TMS that were approximately twice those of sham treatment [O'Readon JP et al. *Biol Psychiatry* 2007]. TMS has been cleared by the FDA as a treatment for patients with unipolar major depression who have had only 1 treatment failure.

Magnetic seizure therapy (MST) uses high-intensity repetitive TMS to induce focal seizures from target regions of the superficial cortex. A potential advantage for MST is that the seizure produced are not as generalized as those produced by ECT, there may be much less memory loss [Spellman T et al. *Biol Psychiatry* 2008].

Deep brain stimulation (DBS) is an invasive technique that uses 3-dimensional MRI to guide the placement of very small wires deep into the brain. Ongoing stimulation is accomplished by a pacemaker-like pulse generator implanted in the chest, which can be controlled by a magnet and a small control box that is outside the patient. It is being investigated as a treatment for patients with chronic TRD who have failed all other therapies as an alternative to creating lesions in the brain [Mayberg HS et al. *Neuron* 2005].

"As we become more invasive, we also become more specific; we may actually be able to target areas for patients who have particular types of depression and possibly decrease side effects," said Dr. McDonald.

Pharmacological Strategies for Treatment-Resistant Depression (TRD)	
Optimization (monotherapy)	Increase the dose or duration, or alter the timing of the primary antidepressant.
Substitution (switching)	Stop first medication, start next one as monotherapy. New drug can be within or across class.
Augmentation	Add a second drug (adjunct) that is not an antidepressant to the antidepressant that has not produced an adequate response.
Combination	Two antidepressants used together, typically for synergistic mechanisms.

Highlights from the
American Psychiatric Association 2009 Annual Meeting