Just the Berries

Pharmacologic management of refractory depression

S. Chehil, MD, MSC S. Devarajan, MD, MRCPSYCH(UK), FRCPC S.M. Dursun, MD, PHD, FRCPC

Major depression is a common and debilitating disorder that affects 10% to 15% of the population each year. Advances in understanding the psychopharmacology of depression has lead to the introduction of several new classes of antidepressant medication in the past decade. Despite these advances, however, patients' overall response to any given pharmacologic approach continues to be unsatisfactory. Only 50% of patients recover fully from depression with antidepressant therapy; 35% to 40% recover partially and continue to have residual symptoms; and 10% to 15% do not improve at all despite adequate trials (diagnosis, selection of medication, treatment time, and compliance) of antidepressant medication.

The clinical importance of these figures is underscored by the fact that incomplete recovery from a primary depressive episode is associated with serious personal, economic, and psychosocial morbidity. Complications include prolonged suffering of patient and family, higher risk of suicide, increased medical and psychiatric comorbidity, loss of productivity, loss of income, erosion of social support, social withdrawal, and increased levels of dependency. Refractory patients, therefore, represent a dilemma for primary care providers.[1-3]

How is refractory defined? One proposed operational definition of refractory depression is a poor or unsatisfactory response to two adequate trials (optimal dosage and duration) of two different classes of antidepressant medication after ruling out possible medical or organic causes of the condition (**Table 1**).

Table 1. Common medical contributors to refractory depression

Endocrine disorders: thyroid disease, hypercortisolism (Cushing's syndrome)
Infections: postviral syndromes (Epstein-Barr, cytomegalovirus, influenza), human immunodeficiency virus
Neoplastic syndromes
Neurologic conditions: previous stroke or recent transient ischemic attack, Parkinson's disease, primary sleep disorders
Autoimmune diseases: systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis
Medication related to depression: vincristine, high-dose benzodiazepines (eg, diazepam >30 mg, clonazepam >1.5 mg, lorazepam >6 mg), steroids (prednisone >40 mg), antihypertensives (high-dose propranolol, atenolol), angiotensin-converting enzyme inhibitors (except captopril), calcium channel blockers, and very high–dose estrogen

Strategies for treating refractory depression include augmentation and combination therapy and switching (changing to a different agent). Although both strategies are currently employed, there are few parallel comparison studies that directly test these two approaches. Interventions, therefore, must take into account the diversity of clinical presentation and be tailored to each clinical circumstance.[1-4]

Switching

Switching therapeutic agents is supported by

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Drs Chehil, Devarajan, and **Dursun** work in the Psychopharmacology Unit in the Department of Psychiatry at Dalhousie University in Halifax, NS.

Table 2. Augmenting agents

AGENT	DOSAGE / DAY	ONSET OF RESPONSE	COMMENTS
Established agent*			
• Lithium	300–900 mg	48 h – 2 wk	Can be used with TCAs, SSRIs, MOAIs, pregnancy tests, TH-Abs, RFT, TFT, and electrolytes
Well established agents†			
• Triiodothyronine	12.5–50 μg	2 wk	Monitor cardiac after effects
• L-Tryptophan	2–5 g	2 wk	Monitor serotonin syndrome
• Buspirone	10–60 mg	2–3 wk	
• Pindolol	2.5 mg twice daily	1–2 wk	Contraindicated in COPD or bronchial asthma
• Methylphenidate	5–40 mg	1–2 wk	Monitor sleep quality, anxiety
Evidence accumulating‡			
• Olanzapine	2.5–5 mg	Not established	Prefer fluoxetine?
• Risperidone	0.5–2 mg	Not established	
• Ketoconazole	200–400 mg (?)	Not established	Monitor LFT, TFT, RFT, ECG, WBC
Open case reports §			
• Aminoglutethimide	250–500 mg?	Not established	Monitor LFT, TFT, RFT, ECG, WBC
• Naltrexone	50 mg?	Not established	Monitor LFT, TFT, RFT, ECG, WBC
• Pergolide	1–5 mg?	Not established	

COPD—chronic obstructive pulmonary disease, ECG—electrocardiogram, LFT—liver function test, MAOIs—monoamine oxidase inhibitors, RFT—renal function tests, SSRIs—serotonin reuptake inhibitors, TCA—tricyclic antidepressants, TFT—thyroid function tests, TSH—thyroid-stimulating hormone, TH-Abs—thyroid hormone antibodies, WBC—whole blood count.

*Criterion standard: evidence level 1A. †Evidence level 1A-2B. ‡Evidence level 2B-3. §Evidence level 3-4.

the data on continuation and maintenance of antidepressant monotherapy and could be favoured for patients whose compliance might be jeopardized by the introduction of polypharmacy with its accompanying risks of adverse events secondary to drug interactions. With switching, however, patients sometimes lose all gains made by discontinuing the first antidepressant medication. Such a setback could be especially important for partial responders, where loss of even small gains might lead to serious consequences.

Augmentation and combination

Augmentation and combination strategies refer to use of two or more agents to target the core symptoms of depression by targeting different neurotransmitter systems, different aspects of neurotransmission, or a combination of these actions. Augmentation strategies involve addition of drugs that are not antidepressants, whereas combination strategies involve addition of antidepressants from a different class. Augmentation and combination approaches are distinguished from adjunctive therapy, which employs a second agent to reverse an emergent side effect or obtain a complementary clinical effect (ie, restricted, short-term use of benzodiazepines for insomnia or symptoms of anxiety).

Despite limited empirical evidence for the efficacy of augmentation and combination strategies, this option holds several advantages over switching. First, patients who do not respond to a first antidepressant might respond when a second agent is added. Second, the strategy builds on therapeutic gains obtained with the first antidepressant. Third, there is potential for rapid onset of antidepressant effect. Response could take as few as 2 days or up to 3 to 6 weeks (considerably shorter than the delay expected with switching, which involves tapering the first drug, wash-out, and delay in onset of effects of the second drug). Last, addition of a second compound is generally well tolerated and does not substantially alter the side-effect profile of the initial antidepressant.

The best studied augmentation strategy has been addition of lithium to a tricyclic antidepressant. Other strategies have investigated the addition of triiodothyronine (T_3), L-tryptophan, buspirone, pindolol, psychostimulants, atypical antipsychotics, and other classes of antidepressants (**Table 2**). Although meta-analysis has supported the effectiveness of lithium

Table 3. Drug combinations and cocktails

Serotonin reuptake inhibitor + tricyclic antidepressant (ie, fluoxetine + desipramine)
Serotonin reuptake inhibitor + bupropion
Tricyclic antidepressant + monoamine oxidase inhibitor (avoid imipramine, desipramine, clomipramine)
Serotonin reuptake inhibitor + noradrenaline reuptake inhibitor (eg, citalopram + reboxetine)
Phenelzine + L-tryptophan + lithium ("Newcastle cocktail")
Nefazodone + pindolol + L-tryptophan ("Dalhousie serotonin cocktail")
Electroconvulsive therapy + pindolol
Nefazodone + venlafaxine
Serotonin reuptake inhibitor + atypical antipsychotic (fluoxetine + olanzapine)

and T_3 augmentation strategies, robust evidence for other strategies is lacking. In addition, empirical data addressing optimal duration of therapy with augmentation agents is not yet available, and it is unclear whether results of trials investigating the efficacy of augmentation in one class of antidepressant can be extrapolated to other classes.[1-11] Augmentation strategies to consider appear in **Table 3**.

Conclusion

Given the limited evidence available at this time, the decision on which strategy to choose or which agents to combine is somewhat arbitrary. One suggestion is to carefully assess unresolved or residual psychopathology and, if possible, to cluster it with correlates within the monoamine system (dopamine, noradrenaline, serotonin) and choose an augmenting or combining agent accordingly. A simplified approach to refractory depression is presented in **Figure 1**.

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Figure 1. Pharmacologic treatment algorithm for refractory depression