Pharmacological treatment approaches to difficult-to-treat depression

Summary

- In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial of almost 3000 patients with depression in the United States, 50% responded to the initial trial of a selective serotonin reuptake inhibitor antidepressant, but only a third achieved remission (nil or minimal depressive symptoms). The final remission rate, even after four potential treatment steps, was only 70%.
- This finding reflects the reality of clinical practice and highlights the need to employ the best available evidence in the management of people with complex depression.
- Before adopting a pharmacological strategy for a patient with difficult-to-treat depression, general clinical issues (such as missed psychiatric diagnoses, unresolved psychological issues and treatment non-adherence) should be considered.
- While there is no strong evidence for the order of implementing evidence-based pharmacological strategies for difficult-to-treat depression, we recommend: i) increase antidepressant dose; ii) switch to different antidepressant; iii) augment with a non-antidepressant agent; and iv) combine antidepressants. Sometimes it may be more appropriate to consider augmentation before switching antidepressants.
- The use of psychological interventions or other physical treatments such as electroconvulsive therapy should be considered at each step in management.

It is widely accepted that at least one in three patients with depression will not respond adequately to a series of appropriate treatments.[1] There have been several approaches to defining this difficult-to-treat depression. One recently developed proposal is the Maudsley staging method — a points-based model of degrees of treatment resistance, which takes into account details of the specific treatments employed and the severity and duration of the depression.[2] Another widely used and more straightforward definition is the failure to respond to two adequate trials of antidepressants from different pharmacological classes.[3]

Here, we use a pragmatic definition of difficult-to-treat depression — failure to respond to an adequate course of a selective serotonin reuptake inhibitor (SSRI) antidepressant. This was the definition used in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial in the United States,[4] which was funded by the National Institute of Mental Health and is the single biggest study on sequenced treatment for depression and investigated rates of improvement in patients who had failed to respond to an SSRI. In this article, we draw liberally on the findings of the STAR*D trial, as well as other studies of difficult-to-treat depression.

STAR*D: a real-world study

The STAR*D trial used a series of treatment steps, premised on an initial failure to achieve remission after an adequate course of an SSRI. This approach reflects the reality of primary care and specialist treatment of depression in Australia (and most countries), whereby most patients who require antidepressants are initially treated with an SSRI. The trial recruited "real-world" patients with depression, including patients who are usually excluded from formal randomised controlled trials (RCTs), such as those with chronic symptoms, comorbid psychiatric and physical disorders, and substance misuse. STAR*D used a four-step approach for each patient, with the three potential steps after the initial SSRI comprising the main options developed over decades for difficult-to-treat depression: switching, augmenting or combining antidepressants. It used "remission" rather than the usual measure of "response" as its outcome. Remission refers to achieving nil or minimal depressive symptoms, whereas response is usually defined as a 50% reduction in symptoms. In clinical practice, both practitioners and patients aim for remission rather than response.

Studying almost 3000 patients, STAR*D found that, although 50% of patients responded to the initial trial of an SSRI, only a third achieved the more clinically meaningful outcome of remission. Furthermore, the final remission rate, even after four potential treatment steps, was only 70% (ie, 30% of patients did not remit with up to four different antidepressant treatment approaches). This finding reflects the reality of clinical practice and highlights the need to employ the best available evidence in the management of people with complex depression.

Two limitations of STAR*D need to be acknowledged: some of the treatment choices used are not approved for the treatment of depression in Australia, and there was a low retention rate of subjects in the latter phases of the trial.

Structuring management

In this article, we cover the main pharmacological strategies used in the management of difficult-to-treat depression (Box 1). The studies we refer to have mainly focused on patients with unipolar depression (major

1 Pharmacological strategies for difficult-to-treat depression

- Increasing antidepressant dose
- Switching to another antidepressant
- Augmenting with a non-antidepressant agent
- Combining therapy with another antidepressant ◆

Herng-Nieng Chan
MB BS, MMed(Psych), Visiting Fellow (Psychiatrist)[1,2]

Philip B Mitchell
AM, MD, FRANZCP, FRCPsych, Professor and Head,[2] and Director, Bipolar Disorders Clinic[1]

Colleen K A Loo
MB BS(Hons), MD, FRANZCP, Professor of Psychiatry[1,2,3]

Samuel B Harvey
MB BS, MRCPsych, PhD, Senior Lecturer in Workplace Mental Health[1,2]

1 Black Dog Institute, Sydney, NSW.
2 School of Psychiatry, University of New South Wales, Sydney, NSW.
3 St George Hospital, Sydney, NSW.

phil.mitchell@unsw.edu.au

MJA Open 2012; 1 Suppl 4: 44–47
doi: 10.5694/mjao12.10495

depressive disorder). While targeted towards people with difficult-to-treat major depressive disorder, some of the recommendations we give may also be relevant to those with difficult-to-treat bipolar depression.

Increasing antidepressant dose

A number of studies have demonstrated the value of increasing the antidepressant dose to the maximum tolerated level approved in the product information. While early RCTs reported the superiority of high-dose fluoxetine (60 mg/day) over some augmentation strategies,[5] later systematic reviews found limited evidence to support high-dose SSRI usage in difficult-to-treat depression.[6] However, there is stronger evidence for the effectiveness of increasing the dose of other categories of antidepressants, particularly tricyclic antidepressants (TCAs) and the serotonin–noradrenaline reuptake inhibitor venlafaxine.[6,7] For some TCAs (but not other antidepressants), monitoring serum levels may be useful in achieving optimal clinical response.

Switching to another antidepressant

There are three main issues to consider with this approach. Is switching to a second antidepressant an effective strategy? Does this switch need to be to a different class of antidepressants? When should a switch occur? Recent evidence has suggested that antidepressants may have a faster onset of action than initially thought,[8] with most guidelines suggesting that treatment changes should be considered if no response is seen after 4 weeks.[7]

After failure to respond to initial treatment with an SSRI, there is strong evidence for switching to another antidepressant, but inconsistent evidence as to whether this needs to be a non-SSRI antidepressant or a different SSRI. One meta-analysis has reported a small but significant advantage (relative risk [RR], 1.29) of switching from an ineffective SSRI to a non-SSRI antidepressant (bupropion, mirtazapine, venlafaxine) compared with a second SSRI.[9] In an RCT, venlafaxine was found to be superior to paroxetine in achieving response and remission.[10] Other studies have reported that patients who had failed a trial with an SSRI responded to TCAs (imipramine,[11] nortriptyline[12]). In an earlier study, patients who did not respond to two tricyclic antidepressants significantly improved with the monoamine oxidase inhibitor tranylcypromine.[13] The STAR*D trial, however, demonstrated no significant differences in response rates between patients who switched to a second SSRI (sertraline) or to other classes of antidepressants (bupropion, venlafaxine).[14] Consistent with this, a large systematic review concluded that treatment response was similar whether patients switched to a second SSRI or another class of antidepressants.[15] Overall, and contrary to intuition, the accumulated evidence suggests no clear advantage of switching to a non-SSRI compared with a different SSRI.

Augmenting with a non-antidepressant agent

Augmentation involves adding a non-antidepressant drug to ongoing antidepressant therapy to which there has been no or only partial response. Here, we review the evidence for several well studied augmentation strategies.

Lithium

The evidence for lithium augmentation of antidepressants is very strong. One meta-analysis found lithium augmentation of TCAs and SSRIs significantly more effective in achieving response than augmentation with a placebo (odds ratio [OR], 3.11; 95% CI, 1.80–5.37), with a number-needed-to-treat of 5.[16] Another meta-analysis reported a number-needed-to-treat of 3.8.[17] Lithium augmentation was less efficacious in the STAR*D trial, but patients were prescribed suboptimal doses because of concern about adverse effects.[18]

Atypical antipsychotics

The atypical antipsychotics studied as augmentation agents include risperidone, quetiapine, olanzapine and aripiprazole. Two meta-analyses have confirmed the efficacy of this strategy. The first included 10 RCTs and concluded that risperidone, quetiapine and olanzapine were effective as augmentation agents (RR, 1.75).[19] The other meta-analysis reported similar findings for aripiprazole (OR, 2.0).[20]

Thyroid hormone (triiodothyronine)

One meta-analysis reported triiodothyronine (T_3) augmentation of TCAs to be twice as likely to achieve response as placebo.[21] A further meta-analysis found that T_3 augmentation significantly accelerated the treatment response of TCAs.[22] A systematic review that included three open-label studies and one RCT supported T_3 augmentation of SSRIs.[23] In the STAR*D trial, remission rates were not significantly different between patients with difficult-to-treat depression whose SSRI was augmented with T_3 or lithium, but T_3 augmentation was associated with a lower side-effect burden.[18] Thyroxine (T_4) augmentation has not been extensively investigated.

Other augmenting agents

Lamotrigine is an anticonvulsant for which there is strong evidence of prevention of depressive recurrences in bipolar disorder.[24] While early clinical reports suggested lamotrigine may have a similar effect in unipolar depression,[25] two RCTs[26,27] and a systematic review[28] have so far failed to demonstrate significant reductions in depressive symptoms in patients with difficult-to-treat depression receiving lamotrigine augmentation.

Methylphenidate is used clinically for depressed patients with significant apathy and fatigue, particularly on the eastern seaboard of the US. Although early open-label studies suggested efficacy, two recent RCTs have reported no significant benefit of methylphenidate augmentation.[29,30]

Modafinil, which is less likely than other stimulants to cause dependence, has also been investigated as a potential augmenting agent, although at present data supporting its use are very limited.[31,32]

2 Clinical factors to consider when assessing a patient with difficult-to-treat depression

- Possible missed diagnoses such as bipolar disorder, major depressive disorder with psychotic features, other psychotic disorders such as schizophrenia, primary anxiety disorders, or primary personality disorders
- Unresolved psychosocial issues (eg, ongoing relationship difficulties or unemployment)
- Treatment non-adherence (consider measurement of serum antidepressant levels)
- Rapid antidepressant metabolism (consider genotyping of relevant metabolising enzymes, such as cytochrome P450 2D6)
- Inadequate antidepressant trial (ie, suboptimal dose and/or duration)
- Comorbid psychiatric illnesses: anxiety disorders, substance use disorders
- Comorbid medical illnesses: endocrine disorders (eg, hypothyroidism), neurological disorders (eg, cerebral neoplasm, multiple sclerosis), autoimmune disorders (eg, systemic lupus erythematosus)
- Concurrent medications: antihypertensives (β-blockers, calcium-channel blockers), steroids, anti-Parkinsonian drugs (bromocriptine, levodopa) or interferon, which may exacerbate depression ◆

Pindolol has been reported to accelerate the speed of response to SSRIs. However, this β-blocker did not enhance the antidepressant action of SSRIs in three RCTs.[33-35]

Combining therapy with another antidepressant

It has been hypothesised that the synergistic effects of two antidepressants with different mechanisms of action may enhance response in difficult-to-treat depression. One of the earliest RCTs to test this theory reported greater efficacy from combining desipramine and fluoxetine, compared with monotherapy with either agent.[36] Mirtazapine added to SSRI therapy was reported to improve outcome in one RCT.[37] However, the widely used mirtazapine–venlafaxine combination was not found to be superior to monotherapy with tranylcypromine in a trial of patients whose depression had failed to respond to three medication trials.[38] The citalopram–bupropion combination yielded similar remission rates in patients with difficult-to-treat depression as those who received augmentation with buspirone.[39]

It should be noted that while bupropion is approved as an antidepressant in the US, it has never been approved for this indication in Australia, where it is only approved for reducing craving on cessation of smoking. Prescribers also need to be aware of the risk of serotonin syndrome when combining two different antidepressants.[40]

3 Pharmacological treatment recommendations for difficult-to-treat depression

1. Increase antidepressant dose
   - The maximum tolerable approved dose should be prescribed for at least 4–6 weeks
2. If nil or partial response, consider switching to another antidepressant
   - Different SSRI
   - Non-SSRI antidepressant (such as venlafaxine or other SNRI, mirtazapine, TCA, monoamine oxidase inhibitor or bupropion*)
3. If nil or partial response, consider augmenting with a non-antidepressant agent
   - Lithium
   - Atypical antipsychotic
   - Triiodothyronine
4. If nil or partial response, consider combining antidepressants
   - SSRI + mirtazapine
   - Mirtazapine + venlafaxine (or other SNRI)
   - SSRI + TCA
   - SSRI + bupropion*

SSRI = selective serotonin reuptake inhibitor. SNRI = serotonin–noradrenaline reuptake inhibitor. TCA = tricyclic antidepressant.
* Bupropion is not approved for the indication of depression in Australia. ◆

Future possible pharmacological strategies

As excessive glutamatergic activity has been hypothesised to cause depression, drugs that modulate *N*-methyl-D-aspartate (NMDA) receptors have attracted interest. Ketamine is an NMDA receptor antagonist, and ketamine infusion has demonstrated rapid (within 4 hours) and significant antidepressant effects in patients with difficult-to-treat depression.[41] Riluzole, which decreases glutamate release and has been shown to be efficacious in treating amyotrophic lateral sclerosis, has shown promise in an open-label study of depression.[42] There have been no RCTs of riluzole in depression or difficult-to-treat depression. Preclinical studies have suggested zinc, a non-competitive NMDA receptor antagonist, may be another augmentation option, but robust clinical trial data are currently lacking.[43] In view of the cholinergic system being implicated in depression, agents that act on acetylcholine receptors are also being investigated. Scopolamine is an antimuscarinic drug that has been reported to significantly relieve depression in patients with major depressive disorder.[44] Mecamylamine is a nicotinic acetylcholine receptor antagonist that showed promise in a preliminary study as an augmentation agent in patients responding poorly to SSRIs.[45]

Treatment recommendations

Before adopting a new pharmacological strategy for a patient with difficult-to-treat depression, some general clinical issues should be considered (Box 2). Furthermore, the use of psychological interventions or other physical treatments such as electroconvulsive therapy (see Casey et al, *page 52*;[46] and Fitzgerald, *page 48*[47]) should be considered at each step in management.

Although there is no strong evidence for the order of implementing pharmacological strategies for difficult-to-treat depression, we recommend the following: i) increase antidepressant dose; ii) switch to different antidepressant; iii) augment with a non-antidepressant agent; and iv) combine antidepressants (Box 3). Sometimes it may be more appropriate to consider augmentation before switching antidepressants, particularly if there has been partial response to the antidepressant treatment. In addition to the benefits associated with each of these options, prescribers need to be aware of the potential for side effects and the need for close monitoring with all of

these strategies. In general, specialist assistance should be sought if augmentation or combining antidepressants is being considered.

Acknowledgements: Philip Mitchell's research is funded by a National Health and Medical Research Council program grant (no. 510135).

Competing interests: Herng-Nieng Chan has not accepted remuneration from pharmaceutical companies and has never been a member of an industry advisory committee. Philip Mitchell has not accepted remuneration from pharmaceutical companies for over 3 years, and has not been a member of an industry advisory committee in that time. Colleen Loo has received honoraria from Pfizer, AstraZeneca, Servier and Eli Lilly for giving educational talks on electroconvulsive therapy and brain stimulation at psychiatric conferences. Samuel Harvey has not accepted any remuneration from pharmaceutical companies for over 5 years and has never been a member of an industry advisory committee.

Provenance: Commissioned by supplement editors; externally peer reviewed.

1 Souery D, Papakostas GI, Trivedi MH. Treatment-resistant depression. *J Clin Psychiatry* 2006; 67 Suppl 6: 16-22.
2 Fekadu A, Wooderson S, Donaldson C, et al. A multidimensional tool to quantify treatment resistance in depression: the Maudsley staging method. *J Clin Psychiatry* 2009; 70: 177-184.
3 Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. *Can J Psychiatry* 2007; 52: 46-54.
4 Rush AJ, Warden D, Wisniewski SR, et al. STAR*D: revising conventional wisdom. *CNS Drugs* 2009; 23: 627-647.
5 Fava M, Rosenbaum JF, McGrath PJ, et al. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. *Am J Psychiatry* 1994; 151: 1372-1374.
6 Adli M, Baethge C, Heinz A. Is dose escalation of antidepressants a rational strategy after a medium-dose treatment has failed? A systematic review. *Eur Arch Psychiatry Clin Neurosci* 2005; 255: 387-400.
7 Anderson IM, Ferrier IN, Baldwin RC, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. *J Psychopharmacol* 2008; 22: 343-396.
8 Posternak MA, Zimmerman M. Is there a delay in the antidepressant effect? A meta-analysis. *J Clin Psychiatry* 2005; 66: 148-158.
9 Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. *Biol Psychiatry* 2008; 63: 699-704.
10 Poirier MF, Boyer P. Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomised comparison. *Br J Psychiatry* 1999; 175: 12-16.
11 Thase ME, Rush AJ, Howland RH, et al. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. *Arch Gen Psychiatry* 2002; 59: 233-239.
12 Nierenberg AA, Papakostas GI, Petersen T, et al. Nortriptyline for treatment-resistant depression. *J Clin Psychiatry* 2003; 64: 35-39.
13 Nolen WA, van de Putte JJ, Dijken WA. Treatment strategy in depression. II. MAOI inhibitors in depression resistant to cyclic antidepressants: two controlled crossover studies with tranylcypromine versus L-5-hydroxytryptophan and nomifensine. *Acta Psychiatr Scand* 1988; 78: 676-683.
14 Rush AJ, Trivedi MH, Wisniewski SR, et al; STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med* 2006; 354: 1231-1242.
15 Ruhé HG, Huyser J, Swinkels JA, Schene AH. Switching antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: a systematic review. *J Clin Psychiatry* 2006; 67: 1836-1855.
16 Crossley NA, Bauer M. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. *J Clin Psychiatry* 2007; 68: 935-940.
17 Bschor T, Lewitzka U, Sasse J, et al. Lithium augmentation in treatment-resistant depression: clinical evidence, serotonergic and endocrine mechanisms. *Pharmacopsychiatry* 2003; 36 Suppl 3: S230-S234.
18 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: 1519-1530.
19 Papakostas GI, Shelton RC, Smith J, Fava M. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. *J Clin Psychiatry* 2007; 68: 826-831.
20 Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am J Psychiatry* 2009; 166: 980-991.
21 Aronson R, Offman HJ, Joffe RT, Naylor CD. Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. *Arch Gen Psychiatry* 1996; 53: 842-848.
22 Altshuler LL, Bauer M, Frye MA, et al. Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. *Am J Psychiatry* 2001; 158: 1617-1622.
23 Cooper-Kazaz R, Lerer B. Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin reuptake inhibitors. *Int J Neuropsychopharmacol* 2008; 11: 685-699.
24 Calabrese JR, Bowden CL, Sachs G, et al; Lamictal 605 Study Group. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* 2003; 64: 1013-1024.
25 Barbee JG, Jamhour NJ, Lamotrigine as an augmentation agent in treatment-resistant depression. *J Clin Psychiatry* 2002; 63: 737-741.
26 Barbee JG, Thompson TR, Jamhour NJ, et al. A double-blind placebo-controlled trial of lamotrigine as an antidepressant augmentation agent in treatment-refractory unipolar depression. *J Clin Psychiatry* 2011; 72: 1405-1412.
27 Santos MA, Rocha FL, Hara C. Efficacy and safety of antidepressant augmentation with lamotrigine in patients with treatment-resistant depression: a randomized, placebo-controlled, double-blind study. *Prim Care Companion J Clin Psychiatry* 2008; 10: 187-190.
28 Thomas SP, Nandhra HS, Jayaraman A. Systematic review of lamotrigine augmentation of treatment resistant unipolar depression (TRD). *J Ment Health* 2010; 19: 168-175.
29 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: 87-94.
30 Patkar AA, Masand PS, Pae CU, et al. A randomized, double-blind, placebo-controlled trial of augmentation with an extended release formulation of methylphenidate in outpatients with treatment-resistant depression. *J Clin Psychopharmacol* 2006; 26: 653-656.
31 DeBattista C, Lembke A, Solvason HB, et al. A prospective trial of modafinil as an adjunctive treatment of major depression. *J Clin Psychopharmacol* 2004; 24: 87-90.
32 Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. *J Clin Psychiatry* 2005; 66: 85-93.
33 Pérez V, Soler J, Puigdemont D, et al. A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. *Arch Gen Psychiatry* 1999; 56: 375-379.
34 Moreno FA, Gelenberg AJ, Bachar K, Delgado PL. Pindolol augmentation of treatment-resistant depressed patients. *J Clin Psychiatry* 1997; 58: 437-439.
35 Perry EB, Berman RM, Sanacora G, et al. Pindolol augmentation in depressed patients resistant to selective serotonin reuptake inhibitors: a double-blind, randomized, controlled trial. *J Clin Psychiatry* 2004; 65: 238-243.
36 Nelson JC, Mazure CM, Jatlow PI, et al. Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind randomized study. *Biol Psychiatry* 2004; 55: 296-300.
37 Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. *Biol Psychiatry* 2002; 51: 183-188.
38 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: 1531-1541.
39 Trivedi MH, Fava M, Wisniewski SR, et al; STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med* 2006; 354: 1243-1252.
40 Pilgrim JL, Gerostamoulos D, Drummer OH. Deaths involving contraindicated and inappropriate combinations of serotonergic drugs. *Int J Legal Med* 2011; 125: 803-815.
41 Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 2006; 63: 856-864.
42 Sanacora G, Kendell SF, Levin Y, et al. Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms. *Biol Psychiatry* 2007; 61: 822-825.
43 Siwek M, Dudek D, Paul IA, et al. Zinc supplementation augments efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. *J Affect Disord* 2009; 118: 187-195.
44 Furey ML, Drevets WC. Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. *Arch Gen Psychiatry* 2006; 63: 1121-1129.
45 George TP, Sacco KA, Vessicchio JC, et al. Nicotinic antagonist augmentation of selective serotonin reuptake inhibitor-refractory major depressive disorder: a preliminary study. *J Clin Psychopharmacol* 2008; 28: 340-344.
46 Casey MF, Perera DN, Clarke DM. Psychosocial treatment approaches to difficult-to-treat depression. *MJA Open* 2012; 1 Suppl 4: 52-55.
47 Fitzgerald PB. Non-pharmacological biological treatment approaches to difficult-to-treat depression. *MJA Open* 2012; 1 Suppl 4: 48-51. ❑