

## TAKE-HOME NOTES:

**The pharmacological treatment of resistant depression – an overview**

Dr Philip J. Cowen

- Treatment-resistant depression is not 'all or none' but is best conceptualised as a series of stages within which patients have failed to respond to an increasing number of therapeutic approaches.
- Many of these stages consist of pharmacological interventions. The present module focuses on pharmacological treatment but other approaches are also important. The use of supportive psychotherapy can help a despairing patient persist in treatment and eventually improve.
- The evidence base for the pharmacological treatment of resistant depression is slight and each patient must be treated on an individual basis in the context of a collaborative and supportive relationship.
- An initial diagnostic assessment should check the diagnosis and other factors such as compliance, substance misuse, and the presence of psychosis. It is also important to determine if patients have bipolar traits (family history of bipolar disorder, personal history of hypomania, hyperthymic personality).
- While these assessments are taking place and if tolerance permits, it is often worthwhile to try increasing the dose of the current medication; particularly if there has been some initial response to treatment.
- The next step is usually to switch medications. For a first switch in a patient unresponsive to SSRI treatment there seems to be little difference in response whether the switch is within class (to another SSRI) or to a drug of a different class.
- Failure to respond to second SSRI should prompt a switch to another drug class, for example, mirtazapine or a tricyclic antidepressant. Amitriptyline and venlafaxine are both somewhat more effective than SSRIs and should be tried at some stage in SSRI non-responders.
- Monoamine oxidase inhibitors (MAOIs) can be helpful in patients who have failed multiple other drug treatments. The reversible type A MAOI, moclobemide, is better tolerated and safer than conventional MAOIs but its efficacy in treatment resistant patients is not well established. It may, however, be worth trying at doses of 600mg and above.
- After switching treatments it is usual to employ antidepressant combinations or augmentation where a drug that is not itself an antidepressant, for example, lithium, is added to the ineffective antidepressant treatment. Lithium augmentation currently has the best evidence base of combination drug treatments in resistant depression and can be combined with all other classes of antidepressants (though caution is needed with SSRIs and SNRIs). However, it is not particularly well-tolerated and requires blood monitoring.
- The aim of antidepressant combination is to provide a spectrum of pharmacological effects. Popular combinations include SSRIs (or venlafaxine) and mirtazapine or SSRIs and reboxetine. Some SSRIs such as paroxetine and fluoxetine slow the metabolism of other drugs and should not generally be combined with tricyclic antidepressants, for example.
- In patients with depressive psychosis it can be very helpful to combine an antipsychotic drug with antidepressant medication. The combination of atypical antipsychotic drugs and SSRIs may be useful in non-psychotic depression but this approach is not currently supported by a good evidence base.
- Patients with bipolar traits can show adverse reactions to antidepressant medication, including the development of mania, rapid cycling and mixed affective states. Such patients may be helped by the use of atypical antipsychotic drugs (with or without SSRIs) and the anticonvulsant drug, lamotrigine.

- Electroconvulsive therapy retains a place in the treatment of drug-resistant depression. However, patients who have failed multiple antidepressant drug treatments have lower responses to ECT and high relapse rates over the next year. ECT can be useful at any stage in very ill depressed patients at high risk of suicide or with poor fluid and food intake.
- Cognitive behaviour therapy can be helpful at all stages in the treatment of resistant depression, and cognitive techniques such as activity scheduling and the modification of negative thinking play an important role in the psychotherapeutic management of chronically depressed patients.

## Figures and tables

[A comparison of venlafaxine with other antidepressants](#)

[Response rate of 51 patients with depressive psychosis to amitriptyline, perphenazine and their combination](#)

[Atypical antipsychotic augmentation: olanzapine](#)

[Atypical antipsychotic augmentation: risperidone](#)

[Atypical antipsychotic augmentation: quetiapine](#)

[Atypical antipsychotic augmentation: aripiprazole](#)

## References

Anderson IM, Nutt DJ, Deakin JFW et al (1993) Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology*; **14**: 3–20.

Bar C, Hotopf M (2001) Amitriptyline v. the rest: still the leading antidepressant after 40 years of randomised controlled trials. *British Journal of Psychiatry*; **178**: 129–44. [\[full text\]](#)

Baldomero B, Ubago G, Cercos JL, et al (2005) Venlafaxine extended release versus conventional antidepressants in the remission of depressive disorders after previous antidepressant failure: ARGOS study. *Depression and Anxiety*; **22**: 68–78. [\[abstract\]](#)

Bauer M, Dopfner S (1999) Lithium augmentation in treatment-resistant depression: meta-analysis of placebo controlled studies. *Journal of Clinical Psychopharmacology*; **19**: 427–34. [\[full text\]](#)

Carpenter LL, Yasmin S, Price LH (2002) A double blind placebo controlled study of antidepressant augmentation with mirtazapine. *Biological Psychiatry*; **51**: 183–88. [\[abstract\]](#)

Crossley, NA, Bauer M (2007) Acceleration and Augmentation of Antidepressants With Lithium for Depressive Disorders: Two Meta-Analyses of Randomized, Placebo-Controlled Trials. *Journal of Clinical Psychiatry*; **68(6)**: 935–40

Goodwin GM (2003) Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology*; **17**: 149–73. [\[abstract\]](#)

Goodwin GM, Bowden CL, Calabrese JR, et al (2004) A pooled analysis of 2 placebo-controlled 18 month trials of lamotrigine and lithium maintenance in bipolar I disorder. *Journal of Clinical Psychiatry*; **65**: 432–41. [\[abstract\]](#)

Himmelhoch JM, Thase ME, Mallinger AG (1991) Tranylcypromine versus imipramine in anergic bipolar depression. *American Journal of Psychiatry*; **148**: 910–16. [\[abstract\]](#)

Kennedy N, Paykel ES (2004) Treatment and response in refractory depression: results from a specialist affective disorders service. *Journal of Affective Disorders*; **81**: 49–53. [\[abstract\]](#)

Marek GK, Carpenter LL, McDougle CJ (2003) Synergistic action of 5-HT<sub>2A</sub> antagonists and selective serotonin reuptake inhibitors in neuropsychiatric disorders. *Neuropsychopharmacology*; **28**: 402–12. [\[abstract\]](#)

National Institute for Clinical Excellence (2004) Depression: Management of depression in primary and secondary care. Clinical Guideline 23.

- Nelson JC, Papakostas GI (2009) Atypical antipsychotic augmentation in major depression: a meta-analysis of placebo-controlled randomized trials. *American Journal of Psychiatry*; **166**: 980–991. [[abstract](#)]
- Nierenberg A, Fava M, Trivedi MH, et al (2006) A comparison of lithium and T<sub>3</sub> augmentation following two failed medication treatments for depression: A STAR\*D report. *American Journal of Psychiatry*; **163**: 1519–1530. [[abstract](#)]
- Poirier MF, Boyer P (1999) Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomised comparison. *British Journal of Psychiatry*; **175**: 12–16.
- Price LH, Charney DS, Heninger GR (1985) Efficacy of lithium-tranylcypromine treatment in refractory depression. *American Journal of Psychiatry*; **142**: 619–23. [[abstract](#)]
- Prudic J, Sackeim HA, Devenand DP (1990) Medication resistance and clinical response to electro-convulsive therapy. *Psychiatric Research*; **31**: 287–96. [[abstract](#)]
- Rush AJ, Fava M, Wisniewski SR (2004) Sequenced treatment alternatives to relieve depression (STAR\*D): rationale and design. *Controlled Clinical Trials*; **25**: 119–42. [[abstract](#)]
- Rush AJ, Trivedi MH, Wisniewski SR, et al (2006) Bupropion-SR, sertraline or venlafaxine-XR after failure of SSRIs for depression. *The New England Journal of Medicine*; **354**: 1231–42. [[abstract](#)]
- Sackheim HA, Prudic J, Devenand DP (1990) The impact of medication resistance and continuation of pharmacotherapy on relapse following response electroconvulsive therapy in major depression. *Journal of Clinical Psychopharmacology*; **10**: 96–104.
- Schatzberg AF (2003) New approaches to managing psychotic depression. *Journal of Clinical Psychiatry*; **64**: 19–23.
- Smith D, Dempster C, Glanville J (2002) Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: meta-analysis. *British Journal of Psychiatry*; **180**: 396–404. [[full text](#)]
- Trivedi MH, Fava M, Wisniewski SR, et al (2006) Medication augmentation after the failure of SSRIs for depression. *The New England Journal of Medicine*; **354**: 1243–1252. [[abstract](#)]