Treatment resistant depression: ten things to do

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Depression that does not remit after two courses of appropriate therapy, given at adequate dose and duration, is referred to as treatment-resistant. The chance of benefit from a first course of antidepressant medication is 50-60%. If this fails, a second course has only a 30-50% chance of success. There are no strongly evidence-based guidelines as to how to proceed at this point. There are however, several important principles to bear in mind:

1. **Is the diagnosis right?** Exclude a substance use disorder, a psychotic illness or a bipolar disorder. Ask about drug and alcohol use, unusual thoughts or experiences and periods of mood elevation or erratic behaviour.
2. **Is the treatment right?** For mild depression, a structured psychotherapy such as CBT is the treatment of choice. If this is unsuccessful, or in more severe depression, an SSRI will normally be the first-line medication. Mirtazapine is another option if sleep or appetite is impaired. For the second trial, consider another SSRI, venlafaxine or duloxetine. Lack of response to one SSRI does not imply lack of response to a second SSRI.
3. **Is the patient taking it?** Adherence rates are poor, with almost 50% of patients discontinuing antidepressant medication within 60 days. Adherence rates to psychological therapies are similarly low.
4. **Is there a history of childhood trauma?** Recurrent self-harm and suicidality, labile mood with frequent anger and unstable relationships all suggest a background of childhood adversity. Consider individual psychotherapy incorporating trauma-focused elements such as dialectical behavioral therapy and mindfulness training.
5. **Exclude organic causes of depression.** Almost all cerebral disorders, and many systemic illnesses, can cause depression, as can some medications such as glucocorticoids. Optimise these conditions as part of your workup of resistantly depressed patients.
6. **Treat co-morbidities vigorously**. This means a focused approach to substance use, which might involve referral to an addiction specialist, anti-craving medication or a 12-step program. Recognise co-morbid anxiety and offer specific treatment, such as referral for cognitive-behavioural therapy.
7. **Methodical, stepwise pharmacotherapy.** Reasonable options after two failed courses of pharmacotherapy include venlafaxine or duloxetine (if not used already), a tricyclic antidepressant (if ingestion is not considered a risk) or MAOI (with adequate education about dietary restriction and interactions). For those bothered by sexual side-effects or weight gain with other agents, consider moclobemide or bupropion.
8. **Augmentation.** The best-studied augmentation agents remain lithium and triodothyronine (T3 – thyroxine is a reasonable substitute). Evidence is accumulating for the (off-label) use of low-dose antipsychosis agents such as olanzapine, aripiprazole and quetiapine. Each of these medications has significant risks associated with its use, which should be discussed in detail with the patient.
9. **Referral.** Cultivate a friendly and helpful psychiatrist, if you can find one. Insist on telephone availability to discuss patients, and reasonably prompt assessment when needed. This should occur for any patient who meets criteria for treatment-resistance, and earlier if there are diagnostic or safety concerns. Consider a tertiary referral centre such as the CADE Clinic at Royal North Shore Hospital or the Black Dog Institute.
10. **Rehabilitation and support.** For patients who do not achieve sustained symptom remission, a rehabilitative chronic illness model is needed. These people really need a good GP, to provide supportive counselling and problem-solving and help them with secondary problems such as smoking, inactivity and weight gain.

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