

Persistent depression

Rethinking the management of treatment-resistant depression.

RECENT approaches to the management of treatment-resistant depression (TRD) involve physical treatments, either alone or requiring augmentation and combination strategies. However, this approach risks some patients being 'over-treated' and other patients 'under-treated'.

TREATMENT-RESISTANT DEPRESSION

This phrase is more a description of a clinical situation than a diagnosis.

Over the past three decades, 'clinical depression' has been viewed as a single condition, varying by severity, and positioned as a 'disease' needing physical treatments.

Therefore, those not responding to a particular physical treatment require a trial of an alternative. This leads to TRD often being diagnosed according to 'staging criteria'.

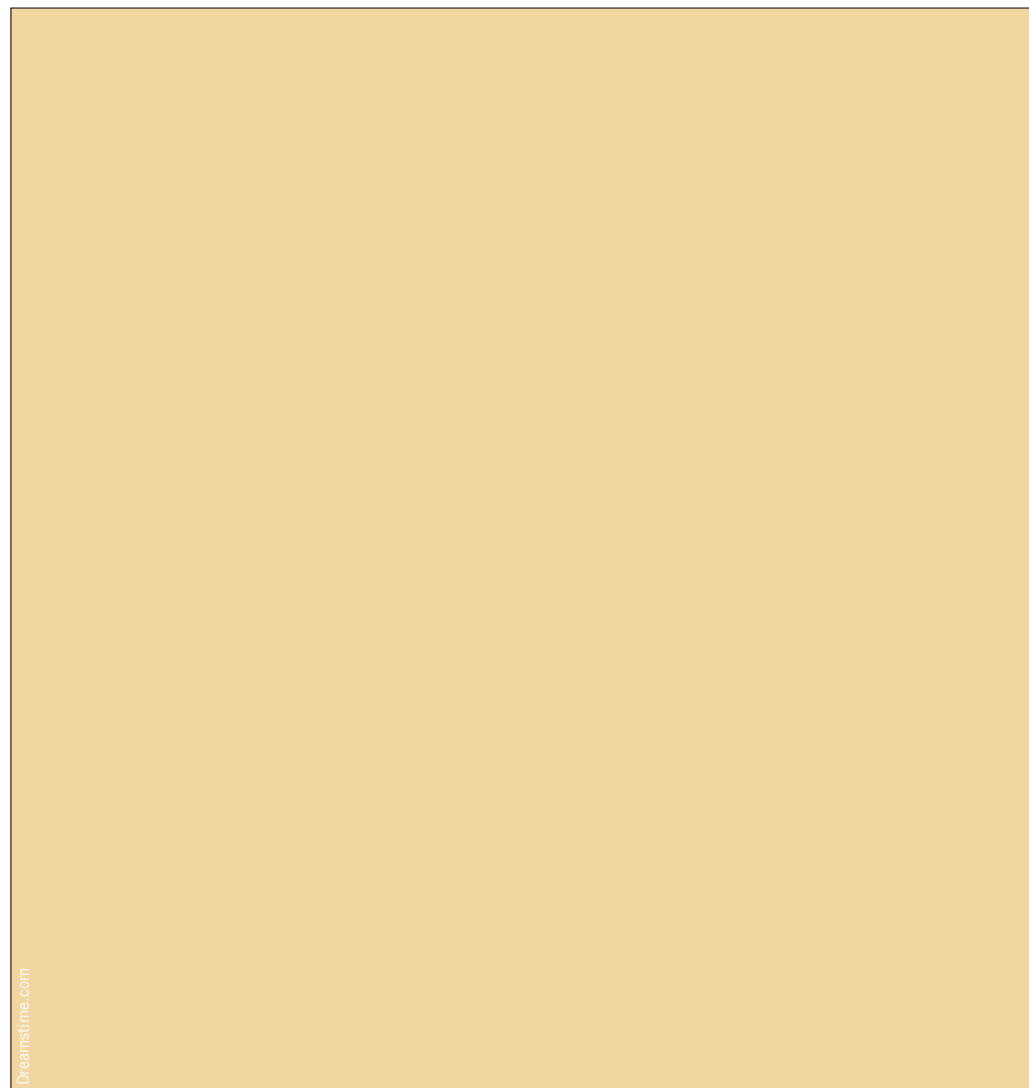
For example, after failing one adequate trial of an antidepressant, the next stage would be trialling a second antidepressant of another class.

For those who fail that stage, the next step would involve broad-spectrum antidepressants, then a combination of drugs or augmentation drugs, and then electroconvulsive therapy (ECT).

As successive trials fail, the diagnosis becomes inevitably TRD.

This approach is evident in the influential Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. This was a US-based 'real world' clinical effectiveness study wherein a large sample of patients with 'major depression' initially received an SSRI antidepressant.

Those who failed to respond received one of four



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alternative treatments (bupropion, sertraline, venlafaxine or cognitive therapy), or SSRI-augmentation (with bupropion, buspirone or cognitive behaviour therapy).

Those who failed to respond to those treatments were next assigned to either nortriptyline or mirtazapine, or to have their current antidepressant augmented with lithium or thyroid hormone.

The remission rates over the stages (documented in numerous publications) were unimpressive, while it is difficult to find support for any other treatment mode once 'resistance' is assumed.

There are many roads to so-called treatment-resistant depression. It can be a true phenomenon (reflecting a range of biological determinants) or for others reflect a situation where a limited dis-

ease-based model has come to dominate diagnosis and management.

AN ANALOGY

To demonstrate this further, consider if the condition under consideration was 'major dyspnoea'.

If it were recommended that this diagnosis required a tried and failed sequence of treatments, from a narrow-action antibiotic to adding a bronchodilator or physiotherapy, then a broad-spectrum antibiotic or augmentation with an antihistamine, and finally an anticoagulant, such an approach would be illogical.

The problem is that major dyspnoea is a symptom that could reflect differing conditions (e.g. pneumonia, asthma, pulmonary embolism).

Any management model

that ignored the nature of the underlying cause would be viewed as untenable, risk both over-treatment and under-treatment, and the condition would be ranked as resistant.

THREE CLINICAL SCENARIOS

1. An elderly man had a strong family history of depression and had had intermittent melancholic depressive episodes, historically responding to the tricyclic, desipramine.

When it was withdrawn from the market, he subsequently failed to respond to a number of newer SSRI antidepressants.

In melancholic depression, there is a greater contribution of noradrenergic and dopaminergic systems, an SSRI may have insufficient potency, and broader-action antidepressants can be more effective. This patient was being under-treat-

ed in not receiving a broad-spectrum antidepressant.

2. A perfectionist school-teacher, criticised in front of the school, developed depression and was immediately trialled on an antidepressant drug. Non-response led to his receiving some 20 psychotropic drugs and two courses of ECT, without benefit.

The likely cause of the teacher's depression is the public 'shaming'. While an antidepressant might ameliorate some of his distress, the causal factor has not been addressed. For instance, if an apology were 'prescribed', rather than medication, he might not have been over-treated and developed a 'resistant' depression.

3. A middle-aged woman was chronically depressed as a consequence of living with a husband who demeaned her and who refused to let her have children, while she also ruminated about episodes of childhood sexual abuse. She failed to respond to multiple psychotropic drugs.

This woman has developed a chronic depression as a consequence of multiple social stresses, and social interventions offer her a superior treatment.

CONCLUSION

Having attended numerous international meetings dealing with TRD, I have been struck by the approach of most 'experts' to manage their patients with a personally preferred and often idiosyncratic set of drug options with little pursuit of the nature of the underlying condition and its cause.

Not all TRD reflects biological origins, and limitations to such a treatment regimen risk 'persistent' rather than 'resistant' depression.

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