PRAXIS

A case of treatment-resistant depression in an older adult and a discussion of treatment options

Emma Pope, 1 D Sabari Muthukrishnan, 2,3 James Phillips, 1,* Sarah Phillips 1,4

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¹Devon Partnership NHS Trust, UK; ²Avon and Wiltshire Mental Health Partnership NHS Trust, UK; ³Kingshill Research Centre, UK

Correspondence to Dr Emma Pope (emmapope1@nhs.net)

*These are pseudonyms for a patient and his wife, who have contributed to the article as authors and with personal reflections but asked to remain

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Treatment-resistant depression is a complex condition often requiring specialist psychiatric care. Many different psychiatric, physical and social factors can lead to a poor response to initial treatment of depression, and a careful assessment is required to determine the most appropriate management option. This can be particularly complex in the older population, who often have multiple physical and social comorbidities. We have used a fictional case to illustrate this, alongside an anonymised vignette of someone with personal experience of this condition. We have also provided an overview of the current evidence for treatment options, as well as a discussion of potential aetiological factors. By the end of this article, readers should understand the ambiguity of this diagnostic term, the aetiological factors that need to be assessed and the rationale for the treatment options available. They should be able to recognise how these ideas apply to the geriatric population.

Keywords Depressive disorders; antidepressants; electroconvulsive therapy; comorbidity; mood stabilisers.

Clinical scenario

You are reviewing a 70-year-old retired teacher, Mr F, admitted informally to a later-life functional ward with a relapse of depression. He has had low mood, anhedonia and fatigue for 4 months, and was admitted following treatment by his community mental health team because of concerns that he has been eating and drinking only when prompted by carers. Until recently he has been independent at home, but his family brought in carers to support his poor self-care when it became too difficult for his disabled wife to manage. This started with support with cooking and cleaning, but they were soon asked to do more for him as his function declined. He shows no evidence of psychosis, but admits to feeling hopeless, and when his family were packing his belongings for admission, they found a collection of tablets with a suicide note and an updated will. He refuses to talk about this and breaks down crying when asked.

He has had depression since his 20s, with five periods of low mood requiring treatment and one admission in his 40s that was resolved with electroconvulsive therapy (ECT). The other episodes initially responded to amitriptyline and later fluoxetine. He has been maintained on fluoxetine for 5 years. When he became unwell, he was switched to sertraline and then venlafaxine with no improvement. He has previously used a course of cognitive-behavioural therapy (CBT) to good effect, but during this bout of illness, he has declined any psychological input.

- What would be your approach to assessment?
- What is treatment-resistant depression (TRD)?
- What common comorbidities are relevant in later-life depression?
- What biopsychosocial factors need to be considered in formulation?
- What other differential diagnoses do you need to consider?
- How should you approach the management of TRD?

Discussion

Definitions of TRD

TRD is a common but complex issue to treat or even define.¹ The most commonly used definition is clinically significant depression that has not responded to two different



treatment courses given at adequate doses and duration,² sometimes with the additional requirement of a course of psychotherapy.¹ If the first definition is used, the sequenced treatment alternatives to relieve depression study (STAR*D trial) estimates that approximately 35% of those with depression have TRD.³ Whatever definition is used, the important principle in clinical practice is to identify individuals for whom their depression is not responding to treatment and look for alternatives.

Approach to treatment

One principle of TRD management is to look for reasons for treatment failure that may then also affect future treatment choices. A list of common issues is provided below, but there are many more, and are patient-specific and multifactorial: 5

- Treatment factors: inadequate dose, inadequate course length and lack of psychotherapy option.
- Patient factors: poor concordance, side-effects, individual pharmacokinetics and medication interactions.
- Psychiatric diagnostic factors: misdiagnosis or comorbidity of bipolar affective disorder, psychotic depression, hypoactive delirium, vascular depression, alcohol and substance misuse, anxiety disorder, personality disorder, post-traumatic stress disorder, emerging dementia and obsessive-compulsive disorder.
- Medical comorbidity: to include hypothyroidism, Cushing's disease, Addison's disease, Parkinson's disease, HIV infection, sleep apnoea and pain. For a more extensive list, please see the referenced review. These conditions can present with low mood, but other conditions (such as diabetes or coronary artery disease) can exacerbate depression through a cycle of low mood leading to poor management of physical health, which then exacerbates the physical symptoms of depression.
- Medications: antihypertensives (one large cohort study suggested that calcium channel antagonists and betablockers increase the risk of depression whereas angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may decrease the risk⁷), steroids, opiates, anti-Parkinsonian drugs and several others. Again, please see the referenced review for a more extensive list.⁶
- Social factors: inadequate or unstable housing or employment, bereavement, social isolation, financial difficulties, uncertainties over immigration status and a variety of types of abuse.
- End-stage disease: in some individuals with highly recurrent disease, early onset or high genetic load, it may be that TRD is the end stage of a more severe illness.

Investigation of these possible causes begins with a thorough history (including developmental and social details) and collateral history, but may also require investigations such as blood tests or neuroimaging. Although some tests are routine and should be done on the majority of patients (e.g. thyroid function tests for hypothyroidism or full blood count for anaemia), others will only be required in certain conditions (e.g. computerised tomography or magnetic resonance imaging scan for dementia, or

dexamethasone suppression test for Cushing's disease). The use of sequential clinical assessment scales can also be invaluable to help to monitor any response to treatment.

Another general principle to consider in older populations is that many patients will be dealing with their depression for the rest of their lives, and as such, any approach to treatment must take account of the chronicity of symptoms rather than just seeking to provide short-term interventions. This includes the impact their illness will have on their carers.

Next steps in treatment

Once the factors above have been considered and managed, the next step is a consideration of possible alternative treatments. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenergic reuptake inhibitors (SNRIs) are usually first- and second-line treatments for depression. We will now consider some of the alternatives available (in no particular order) if these first choices do not provide an adequate response:

- Lithium: one of several first-line agents used to augment antidepressants in unipolar depression.9 It is usually titrated to a plasma level of 0.4-0.8 mmol/L with the scope to increase to a maximum of 1.0 mmol/L. This is supported by National Institute for Health and Care Excellence (NICE) guidance. 10 One 2014 meta-analysis 11 highlighted that many of the trials of lithium augmentation were completed with tricyclic antidepressants. Given that these are now less commonly used as a firstline agent, the meta-analysis aimed to compare this with trials using newer agents. Although the analysis was small (237 patients), it showed that the benefits of lithium augmentation are seen when paired with multiple different antidepressants. Importantly for this case, there is also some limited evidence¹² that lithium augmentation is as effective in older adults as in younger patients. However, in older populations, the rates of side-effects from lithium are higher. 13 Although the evidence suggests lithium can be effective for some, the need for regular blood tests, increased vigilance when physically unwell or dehydrated, and the risk of toxicity if not closely managed, all mean that lithium is not appropriate for every patient. Caution should be used in those with pre-existing kidney or thyroid disease or who are otherwise at high risk of intercurrent illness that could cause dehydration. Lithium also interacts with a wide range of medications that are frequently used in later life, so in cases of polypharmacy, a discussion with the pharmacy team may be of benefit.
- Second-generation antipsychotics: quetiapine, aripiprazole and olanzapine all have good-quality evidence supporting their use to augment SSRIs and SNRIs in TRD, and can be used dependent upon patient-specific factors such as physical comorbidities. For example, one randomised double-blind trial¹⁴ compared olanzapine, fluoxetine and combination therapy in 605 patients with TRD. It showed modest but statistically significant differences in response, with remission rates of 27% for combination treatment, 17% for fluoxetine and 15% for olanzapine over

an 8-week period. The main drawbacks of this option are side-effects such as weight gain and cardiometabolic syndrome, but in select patients there is growing evidence of the utility of antipsychotics. Risperidone is another alternative, although the evidence to support its use is weaker and so would be considered as a second-line treatment.

- Mirtazapine: can be used as a monotherapy or in combination with SSRIs or SNRIs. There is evidence that these particular combinations are more effective than other antidepressant combinations.¹⁵ Patients should be warned about the theoretical risk of serotonin syndrome and specific side-effects should be monitored for, including weight gain and sedation. The latter makes mirtazapine an attractive choice in those suffering from insomnia, where sedation can be beneficial.
- Other antidepressants: although SSRIs and SNRIs have displaced older antidepressants as first-line treatments, tricyclics and monoamine oxidase inhibitors remain useful options, although various guidelines would recommend that other options listed here be tried first. Various papers have been published to this effect, but medications such as imipramine are often not as well-tolerated as more recently developed drugs such as sertraline. 16 The STAR*D report showed only a 6.9% remission rate when tranylcypromine was used after three previous failed trials of medication, and it was not as well-tolerated as a venlafaxine/mirtazapine combination.¹⁷ As with many of the listed treatments, these medications show significant benefit in a minority of patients, but it has proven difficult to predict outcomes before trialling medication. However, tricyclic toxicity means that they must be used with caution, especially in individuals with a high risk of overdose. It is also worth noting that many trials, including STAR*D with its upper age limit of 75 years, exclude older patients, and so many recommendations in the older population are partially based on trials with younger patients. Other antidepressants such as moclobemide and vortioxetine can also be considered, with vortioxetine being a popular choice in certain countries across the globe such as Australia,8 as well as being suggested as an alternative treatment by the NICE.¹⁸
- Psychotherapy: a Cochrane review from 2018¹⁹ collated data from six trials (*n* = 698) comparing usual care with or without psychotherapy. The modalities used included CBT, intensive short-term dynamic psychotherapy, interpersonal therapy and group dialectic behavioural therapy. The study concluded that there is moderate-quality evidence to support the efficacy of psychological therapies in TRD, based upon self-reported and objective measures. However, most of the studies were small so this conclusion largely came from one study on CBT. The authors also highlighted that there were no available studies comparing response rates of psychotherapy to a change in medication.
- ECT: ECT continues to be shown to be an effective alternative to medication in treating depression, with meta-analysis evidence that it is superior to simulated ECT, placebo and various antidepressants. However, given its invasive nature, ECT is usually only used in life-threatening circumstances or after several other failed treatments. This is in line with current NICE guidance, and its use should ideally only occur following a clear and detailed discussion of its risks and benefits with the patient.

There is also some evidence of increased efficacy in treating suicidal intent in the context of unipolar depression in older adults versus younger adults. ²¹ Rarely, where there is an acute response to ECT but this is not maintained with solely pharmacological and psychological treatment, maintenance ECT may be discussed. The ECT minimum dataset for the UK for 2016–2017²² reported that across the 76% of centres that supplied data, there were 141 patients undergoing maintenance ECT for recurrent symptoms of depression. This represents about 8% of those undergoing ECT in total, and so is a relatively uncommon use of ECT. As a result, evidence for its efficacy is sparse and largely relies upon case reports. Despite this, with specialist assessment, this remains a viable treatment option.

• Others: there are several other possible treatment options that are either currently available or being investigated. These include transcranial magnetic stimulation,²³ ketamine, esketamine,²⁴ bupropion augmentation²⁵ (listed among first-line choices by the Maudsley prescribing guidelines⁹), thyroid hormone,²⁶ deep brain stimulation,²⁷ vagus nerve stimulation,²⁸ psilocybin²⁹ and anti-inflammatories.³⁰

As there are many treatment options, decisions should be patient-specific and made collaboratively. If a patient is so severely ill that they lack capacity, a full discussion may not be initially possible, but can be conducted when their condition improves. Of note, there are various patient aids being developed to help with patient access to easily understandable information.³¹

In complex cases, a multidisciplinary approach becomes important. On wards, nurses and support staff who often spend a lot of time with the patient may be able to help support them in understanding the information discussed, and pharmacists can assist with anticipating and advising on potential interactions in the context of polypharmacy. If more specialist advice is needed, a referral to a specialist centre for TRD, such as that run from the Maudsley Hospital, can be considered for a second opinion.

Given that TRD is a chronic condition, thought also needs to be given to how long to continue a treatment when it is successful. Guidance generally suggests that at least 6 months of post-recovery treatment is needed to reduce the risk of immediate relapse. Whether to continue to maintenance treatment to prevent recurrence is patient-specific. This decision will depend upon factors such as the number and severity of previous episodes, the likelihood of recurrence, the patient's wishes, comorbidity and whether there are any persistent depressive symptoms. These need to be balanced against the ongoing risks of the effective medication, which is particularly important in the elderly population, who are often subjected to polypharmacy.

How does this apply to our patient?

There are many different treatment options for TRD, and studies directly comparing them mostly show limited differences in efficacy. However, clinical experience demonstrates that efficacy of each treatment varies significantly in individual cases, but it remains difficult to predict individual responses. Therefore, the decision becomes patient-specific

and depends upon many factors, e.g. current severity of symptoms and risk, comorbidities, patient preference and previous treatment successes or failures. To illustrate this, we return to the case outlined above. Box 1 also provides reflections from our patient and family co-authors on their experience of this disease.

The first steps in Mr F's assessment were a thorough history, collateral history, physical examination and blood tests. This informed an initial risk assessment that established the need for admission owing to suicide risk and selfneglect, a management plan that included continuous line-of-sight observation, food and fluid chart and a multidisciplinary team discussion of how to support him with eating and drinking. This was successful and, with support, he was able to maintain a safe oral intake, allowing time for the team to consider the other aspects of his previous treatment and why his depression had failed to respond to them.

His wife had administered his medication for the previous 3 months, with no missed doses or side-effects. He was given sertraline 150 mg for 7 weeks followed by venlafaxine 225 mg for 6 weeks, with no improvement. This ruled out nonadherence, inadequate doses or treatment length as reasons for the lack of response. He was on no other medication that could have caused an interaction and had a past medical history of well-treated, diet-controlled type 2 diabetes mellitus and chronic kidney disease stage 3, with an estimated glomerular filtration rate of 45 ml/min/1.73 m². An initial physical assessment, including blood tests such as a full blood count, thyroid screen, haemoglobin AIC, fasting glucose and vitamin B12, were all normal. He had no other symptoms to suggest an unknown physical comorbidity. He retired 2 years before admission, but before he became unwell, he had been enjoying retirement and had remained busy redesigning their garden and co-running a local men's social group. His relationship with his wife was happy, with no children, and they had an ageing Labrador whom Mr F would take on daily walks. His wife reported no use of illicit drugs or alcohol.

Over the next several weeks, Mr F was monitored for signs of comorbid psychiatric disorders. There was no evidence of anxiety or psychosis, and a collateral history ruled out the presence of any residual dysthymia or emotional instability between episodes of depression. He was

Box 1. A patient and their family's experience of treatment-resistant depression (consent was given by both the patient and their wife for their contributions to be used).

From Mr Phillips: 'I felt severely anxious and was very agitated with a great loss of confidence. Also, very irrational, I couldn't concentrate and catastrophized about everything. No amount of reassurance from my family helped. Yet, at times in hospital, I was completely lucid, feeling that I had no control of my life and felt very emasculated and inadequate. I also felt my reputation was being damaged by being sectioned'

From Mrs Phillips: 'We were in complete despair, frightened and totally shocked to see such a change in him; no-one could believe that the man they once knew who was decisive and intelligent could have changed so drastically and suddenly...I have been so grateful to the ward team for all their care and attention, persevering to find the correct medication for him...Thank God for the NHS!'

noted to be forgetful and found it difficult to concentrate on tasks such as reading the newspaper. Given his age, dementia was considered a possibility. However, these concerns had only been noted months after his low mood began, so it was initially felt likely that any cognitive symptoms were secondary to the affective disorder. This was confirmed when he was followed up after discharge, when repeat cognitive testing showed no residual deficits.

When completing this assessment, the team met with Mr F and his wife to discuss management options. The first step recommended was combination therapy of venlafaxine 225 mg (his medication on admission) and mirtazapine titrated up to 30 mg. This was based upon evidence showing its efficacy and that Mr F was struggling to sleep. The potential weight gain side-effect was felt to be likely beneficial given his poor appetite. Alongside this, Mr F agreed to meet with the ward psychologist for assessment. It was hoped that this might give him the opportunity to talk about his stockpile of pills and suicide note.

Other possible options considered included lithium or antipsychotic augmentation and ECT. Lithium was not chosen because of his history of chronic kidney disease stage 3. Although there is increasing debate around the potential safety of the use of lithium in chronic kidney disease,³³ for Mr F it was felt that there were better initial alternatives. A second-generation antipsychotic was not chosen because of his diabetes. Finally, ECT was considered at this early stage because of the severity of his presentation and its efficacy during his previous admission. However, it was discounted as he was not yet in a life-threatening situation that would warrant its immediate use and his wife was concerned about the potential effect it would have on his memory. Given that both research and the patient's own history show how effective a treatment it can be, if his initial treatment plan had failed, ECT would likely have been the next step in management. In this instance, he responded to the supportive ward environment, which gave the team time to trial medication-based treatment, but this must be a decision that is tailored to each individual and their circumstances.

It is not uncommon for older adults to have received treatment for depression with tricyclics earlier in life. As the individual moves through life, the tricyclic may be switched to a newer antidepressant with a better safety profile, or stopped because of a lack of ongoing clinical need. However, if tricyclics were well-tolerated and effective, they can be revisited with due caution around potential cardiac side-effects and risks if used in overdose. Mr F had previously been treated successfully with amitriptyline. In this instance, it was not felt to be suitable because he was suffering from a significant postural blood pressure drop and the team were concerned that amitriptyline would exacerbate this and increase his risk of falls.

Mr F tolerated the combination therapy well and, after a period of initial reluctance, he engaged in CBT, where he talked about his suicidal thoughts and overwhelming feelings of guilt that as a retiree he was no longer contributing to society. Regular assessment including use of the Montgomery–Åsberg Depression Rating Scale showed slow but steady improvement. He began to eat and drink and to enjoy engaging in social activities on the ward. He was discharged home on venlafaxine and mirtazapine with regular follow-up and ongoing psychology with his original community mental health team.

Conclusion

This fictional case highlights the complexity of managing TRD with treatment tailored to specific patient characteristics and personal preference. Good management depends upon a thorough history and assessment with collateral taken from family, and a collaborative approach that includes the patient and their family. Decisions can be made easier by a ready understanding of the current literature and clinical guidance, combined with discussion with medical and multidisciplinary team colleagues. The case also highlights the issues of excluding comorbidities and other confounding diagnostic factors. There are several newer treatment options currently being developed that offer hope for the future of the treatment of what can be a life-changing but ultimately often treatable illness. However, much of the evidence base remains focused on younger adults and there is a need for further large studies looking specifically at the older adult population.

About the authors

Emma Pope, BA, BMBCh, MRCPsych, is an ST4 Older Adult Psychiatric Trainee working with the South Devon Older Person's Mental Health Community Team at Devon Partnership NHS Trust, UK. **Sabari Muthukrishnan,** MBBS, DPM, MRCPsych, FHEA, is a Consultant Old Age Psychiatrist with Swindon inpatient services at Avon and Wiltshire Mental Health Partnership NHS Trust, UK; and Principal Investigator for a range of studies at Kingshill Research Centre, UK.

Supplementary material

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Author contributions

E.P. was primary author of text, researched for evidenced literature and coordinated the other authors. S.M. supervised and reviewed the text with alterations suggested, and liaised with J.P. and S.P. J.P. and S.P. provided a review of the text with suggestions of changes from a patient's perspective, and reflection on a patient's experience.

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Declaration of interest

None.

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EDUCATION AND TRAINING

The core trainee 'residential': an opportunity for trainees to feel connected in a world of virtual teaching

Angharad de Cates,¹ Victoria Lane,² Erin Turner³ ©

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¹University of Oxford, UK; ²Birmingham Women's and Children's NHS Foundation Trust, UK; ³Birmingham and Solihull Mental Health NHS Foundation Trust, UK

Correspondence to Erin Turner (erin. turner@nhs.net)

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0/), which permits unrestricted re-use, distribution, and reproduction in any medium, provided the original work is properly cited.

MRCPsych courses play a key role in helping trainees prepare for Membership examinations and specialist training. Historically, their social aspect, although arguably as important, has perhaps not been sufficiently prioritised. During a pandemic, when teaching is largely delivered virtually, the social benefit of meeting peers is highlighted by its absence. Given the future likelihood of increased virtual teaching, it is of paramount importance to explore ways of enhancing the sociability of teaching courses. In addition to the social needs of trainees, there is a recognised need to increase and integrate the neuroscience component of the curriculum to better meet the needs of modern day mental health research, treatment and practice. This article describes how the Birmingham MRCPsych course successfully addressed both these issues with a 2-day 'residential' in October 2019, and considers whether future residentials could be delivered virtually.

Keywords Education and training; trainee support; virtual learning; cognitive neuroscience; residential.

The Birmingham MRCPsych course has a proud tradition of delivering high-quality and innovative teaching from local experts alongside a strong patient and carer contribution.¹ The course has evolved in response to trainee feedback, with a greater emphasis on Clinical Assessment of Skills and Competencies (CASC) practice and preparing CT3

trainees for higher training. However, reports emerged that some trainees found it difficult to get to know their peers during teaching, because of minimal opportunity for social interaction. The sense of isolation induced by a course that is perceived as 'unfriendly' is perhaps most potent for international medical graduates, those returning after prolonged