DOI: 10.1111/bdi.13490

CLINICAL CURIOSITY

BIPOLAR DISORDERS WILEY

Treatment resistant but not irremediable

Gin S. Malhi[1,2,3,4] | Erica Bell[1,2] | Uyen Le[1,2] | Philip Boyce[5] | Michael Berk[6]

[1]Academic Department of Psychiatry, Faculty of Medicine and Health, Northern Clinical School, Kolling Institute, The University of Sydney, Sydney, New South Wales, Australia

[2]CADE Clinic and Mood-T, Royal North Shore Hospital, St. Leonards, New South Wales, Australia

[3]Department of Psychiatry, University of Oxford, Oxford, UK

[4]Oxford Uehiro Centre for Practical Ethics, Faculty of Philosophy, University of Oxford, Oxford, UK

[5]Specialty of Psychiatry, Faculty of Medicine and Health, Westmead Institute of Medical Research, University of Sydney, Sydney, New South Wales, Australia

[6]IMPACT Institute, Deakin University, School of Medicine, Geelong, Victoria, Australia

Correspondence
Gin S. Malhi, CADE Clinic Level 3, Main Hospital Building, Royal North Shore Hospital, NSW 2065, Australia.
Email: gin.malhi@sydney.edu.au

Funding information
Janssen Australia, Grant/Award Number: ACTRN12623001068651 NSLHD

In decades gone by, of the many pharmacotherapeutic strategies that have been trialled to overcome non-response when managing depression, three have stood the test of time. The first, is to optimise the prescribed antidepressant by increasing its dose while maintaining tolerability, the second is to switch to a different class of antidepressant, and the third is to augment antidepressant action by adding an agent that enhances its effect. In some cases, the augmenting agent may exert a synergistic, and independent antidepressant effect. Medications that enhance noradrenergic and dopamine neurotransmission, in addition to enhancing serotonergic activity, such as high-dose venlafaxine and tricyclic antidepressants have long been known to be effective in overcoming non-response.[1] However, this strategy is not always effective and in such instances, the management paradigm then changes to third-line agents like monoamine oxidase inhibitors or, to physical treatments such as electroconvulsive therapy (ECT). In most cases, the MiDAS paradigm, (which denotes Medication, Increase in Dose, Augmentation, and Switch) is effective,[1] however, occasionally nothing seems to work, or if it does its effect does not last. It is this instance of seemingly irremediable depression where multiple treatments have been trialled that is the focus of this case. With increasing chronicity and repeated treatment failures, there is a risk of growing loss of hope, instilling a sense of futility that is difficult to reverse. And yet, as we shall show, even when all avenues have been trialled, improvement is possible—suggesting that genuine treatment resistance that is complete and immutable is extremely rare.

1 | CASE PRESENTATION

A severely depressed white male (ET) just embarking on his seventh decade of life with a long-standing history of treatment non-response—designated early in the course of his illness as having treatment resistant depression (TRD), presented with anxiety that he had self-managed over the years mostly with alcohol. At its nadir, his depression manifests with melancholic features, precipitated by flashbacks of work-related trauma, as a consequence of which he also acquired a diagnosis of post-traumatic stress disorder (PTSD). In addition to his psychiatric conditions, he had developed benign prostatic hyperplasia (BPH) and idiopathic hypertension and, over the years, had undergone several surgical operations including bilateral hip replacement and carpal tunnel release. On top of this, in 2018 (5 years prior to his current presentation), he became briefly addicted to OxyContin following an injury but managed to wean himself off within a matter of months. Since then, he has had no further illicit substance misuse but does smoke tobacco several times a day and drinks excessively—often up to 7 units of alcohol on most days. In this regard, it is important to note that there is a family history of alcohol use disorder but nevertheless he denies craving or experiencing any symptoms of withdrawal and he is able to readily abstain for several days if need be. Importantly, he does have a family history of bipolar disorder, and depression in immediate relatives that has necessitated ECT treatments.

Throughout his life, ET has experienced depression characterised by low energy, weight loss and extensive rumination comprising self-blame and guilt that eventuates in loss of hope and suicidal ideation along with marked agitation. He reports he *'feel[s] miserable especially in the morning'* and in addition to marked diurnal variation of mood, on most days, ET has pervasive anhedonia and a complete loss of libido. However, despite his depression having melancholic features, his illness has also often been exacerbated, and maintained by, social, interpersonal and environmental factors. Indeed, his depression first emerged over 30 years ago in the context of marriage difficulties. At that time, his depression was initially treated with an SSRI (sertraline) by his general practitioner (GP), he was subsequently switched to antidepressants from different classes, with varying degree of partial response and hence why he also underwent augmentation strategies (See Figure 1). Remarkably, and partly because of his stoic personality, he managed to be able to work despite never achieving full remission, although he had periods when he seemed to have some benefit.

More recently, in 2022, having trialled multiple medications, ET was referred to a psychiatrist who prescribed 30 treatments of repetitive transcranial magnetic stimulation (rTMS). He experienced no benefit from rTMS both during the course of treatment and after, and therefore, he was commenced on amitriptyline and olanzapine, which he has maintained to the present day. Having commenced new medications to no avail, ET also underwent ECT in 2022 but he received only seven treatments because of acute cognitive side effects. Early in the following year, as his depression worsened once again, ET underwent a further course of rTMS this time comprising 15 treatments; again, rTMS was of no benefit.

Thus, having trialled all manner of treatments without much success, ET was referred to the CADE clinic[i] (a specialist Mood Disorders Clinic) as a potential participant for our 'Positioning of Esketamine Treatment' (PoET) study in 2023. Upon assessment, he was deemed suitable and enrolled after providing informed consent. As per our protocol, ET received twice weekly esketamine treatment for 4 weeks (See Figure 1 for dosages). His psychotropic medications (amitriptyline 200 mg and olanzapine 10 mg) and others that he took for lowering his cholesterol and controlling his hypertension were unchanged while he received esketamine; his blood pressure was closely monitored and remained stable throughout.

A baseline questionnaire was completed by ET prior to starting intranasal esketamine treatment (56 mg) in mid-February 2024. ET received his last intranasal esketamine treatment (84 mg) in mid-March 2024. In total, he received eight intranasal esketamine treatments and completed weekly questionnaires which included standard depression symptom scales, along with daily questionnaires that rated his mood throughout the duration of the study. Additionally, a comprehensive post-treatment questionnaire was completed after the 4-week trial finished.

Key Message

In a case of long-standing, complicated major depression, esketamine was added to typical therapeutic agents used to overcome non-response. This case exemplifies how even in severe depression that has failed to respond to extensive treatment with diverse interventions, substantive improvements remain possible. Thus, depression described as 'treatment resistant' should not necessarily be regarded as irremediable.

2 | DISCUSSION

During the in-clinic esketamine treatments, ET experienced side effects such as transient increased blood pressure, dizziness and mild dissociation. All these side effects were expected and resolved spontaneously within the 2 h post-treatment observation period. Soon after commencing esketamine, ET reported *'feeling hopeful'* and described his experience as *'one of profound gratitude for life'*.

Upon completion of the acute phase of treatments, ET attended a follow-up assessment 3 weeks after his last esketamine treatment. ET reported that he felt an improvement in his mood after the last treatment and had *'a sense of where I am in life'* and described it as *'the best I've been in years'*. An improvement in mood was also observed by his family and friends. Specifically, he experienced an increase in motivation, hopefulness, self-esteem and a general sense of optimism. The effects were sustained for 10 days post-treatment completion but then his mood dropped at this point. ET reported he had been working part-time and exercising regularly but that he still had *'too much time on hands'*. Overall, prior to esketamine treatments, ET scored 28 on the Montgomery-Asberg Depression Rating Scale (MADRS) and 17 on the Hamilton Depression rating scale (HAM-D). After 4 weeks of esketamine treatment, he scored 18 and 13 on these two scales respectively (improvements of 10 and 4 points on each scale). In addition, ET's Global Improvement score as measured using the Clinical Global Impressions (CGI) scale was rated as a 3 (out of 7) following esketamine treatment. Despite the benefits with short-term therapy, it is important to note that there may be adverse effects long term that require separate, more detailed investigation.

2.1 | Tricyclics, ECT and rTMS

This case highlights the importance of maintaining hope and persistence in the face of apparent resistance. The analyses from the STAR-D study provided pessimistic messaging about the probability of response in depression. This has been rebutted by a recent reanalysis of the data which excluded people who had failed treatment prior to study entry. They found a much more optimistic cumulative

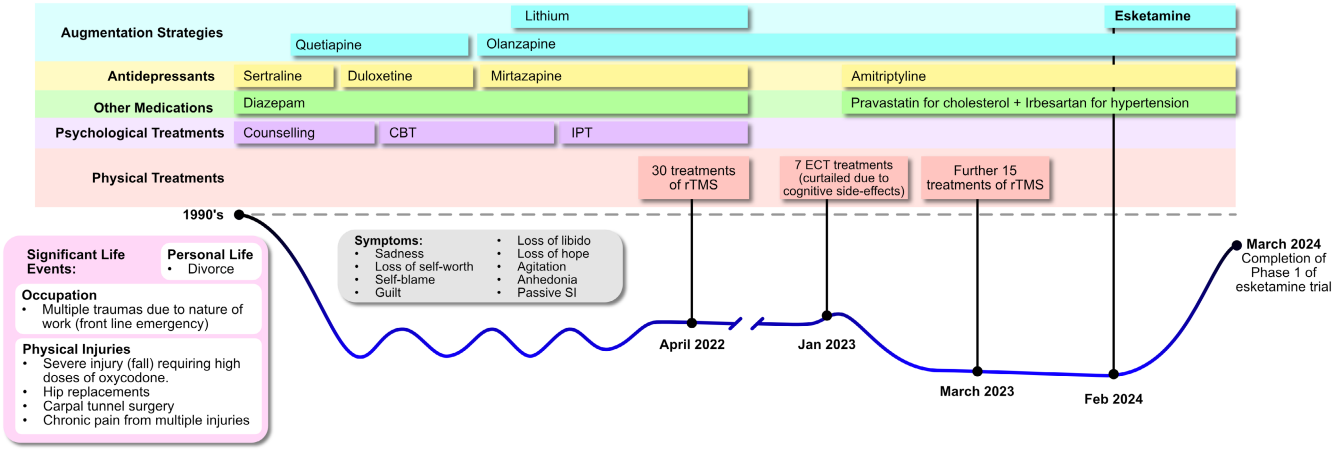

FIGURE 1 Life chart of mood symptoms and treatments. This life chart shows the significant life events and the various interventions trialled by the patient during his depressive episode. His depressive symptoms are shown in the grey box (SI = suicidal ideation). The interventions are categorised according to their modality (i.e. psychological and physical treatments) and the medications are categorised by their type and relationship to one another (i.e. antidepressants, augmentation strategies and other medications). The chart approximately tracks ET's mood and comprises two periods, which vary in time scale. Reference dates are shown as black dots. The first period spans approximately 30 years, from the 1990s to 2022, wherein ET trialled a number of psychological treatments, antidepressants, augmentation strategies with varying levels of partial response, as well as 30 treatments of rTMS which provided no benefit. Please note, the order and duration of treatments shown are approximate, based on the patient's recollection and medical records over this time. The second period spans from early 2023 to March 2024, wherein the patient trialled ECT and showed some response, but this was ceased after seven treatments due to cognitive side effects. Following this, ET received a further course of rTMS which again provided no benefit. The patient was then trialled on amitriptyline combined with extant olanzapine as an augmentation strategy, before being referred to the Positioning of Esketamine in the Treatment of Depression (PoET) Study. The patient received twice weekly administration of esketamine for 4 weeks, with a total of eight doses administered (56 mg × 2 for the first week, followed by 84 mg × 2 for the remaining 3 weeks). The mood line shows ET's improvement over the course of esketamine treatment.

remission rate of 53.8% at 90 days, 74.5% at 180 days and 87.5% at 360 days[2]—contrasting with the original published cumulative remission rate after four treatment steps of 67%. A further key clinical element is persistence. This is emphasised by a contemporary report that those who persisted with up to 10 different treatments developed clinically substantive clinical improvement.[3] Additionally, people who obtained specialised, multi-sector care had a greater probability of being improved 'a lot'.

The failure of ECT to produce an adequate response illustrates the refractoriness of ET's illness. Of some concern, established evidence-based mainstream treatments with proven efficacy for depression with melancholic features, such as tricyclic antidepressants or monoamine oxidase inhibitors or lithium augmentation had not been trialled.[4] A major concern was prescribing a second course of rTMS, which has a limited evidence base,[1] and after failing to respond with ECT.[5] Importantly, his treatment history shows that he was able to achieve fleeting, unsatisfactory benefit from some medications, but these improvements were both insufficient and short-lived. Nevertheless, the fact that even transient improvement occurred revealed that there remained a possibility for improvement, even after so many different trials of treatments had either failed or could not be administered because they were intolerable. Thus, even in circumstances where the illness has marked melancholic features, is resistant to several classes of medications, combinations and augmentation strategies and even ECT and becomes chronic, the possibility of achieving a response remains and the depressive illness is not necessarily irremediable.

The improvement ET experienced following esketamine administration may be due to its unique glutamatergic mechanism of action. It is an antagonist of the ionotropic glutamate receptor (N-methyl-D-aspartate [NMDA]), and its actions on NMDA receptor-mediated signalling are thought to excite pyramidal neurons and increase prefrontal cortex synaptic numbers. This action, alongside the release of striatal dopamine and an increase in activity in reward circuitry, putatively contributes to its antidepressant effects, although its precise mechanism of action in this regard is not fully understood.

3 | CONCLUSION

While not a common example of depression, ET's case is not rare. His history is complicated because of both medical and psychiatric comorbidities and because his illness has been extremely longstanding. This case is interesting because it highlights how even in severe depression where the individual has been correctly diagnosed and undergoes extensive treatments, both pharmacotherapeutic and physical, there is still a possibility of response and an improvement in functioning. Therefore, we suggest that treatment resistance should not be conflated with depression that is irremediable, even in patients for whom ECT has failed, and provided the patient is willing to engage and persist in treatment—this should be considered, and all possible evidence-based options should be actively sought.

ACKNOWLEDGEMENTS

G.S.M. has received grant or research support from National Health and Medical Research Council, Australian Rotary Health, NSW Health, American Foundation for Suicide Prevention, Ramsay Research and Teaching Fund, Elsevier, AstraZeneca, Janssen-Cilag, Lundbeck, Otsuka and Servier; and has been a consultant for AstraZeneca, Janssen-Cilag, Lundbeck, Otsuka and Servier. He is the recipient of an investigator-initiated grant from Janssen-Cilag (PoET Study), joint grant funding from the University of Sydney and National Taiwan University (Ignition Grant) and grant funding from The North Foundation. E.B. has received joint grant funding from the University of Sydney and National Taiwan University (Ignition Grant) and grant funding from The North Foundation. U.L. is employed through funding from an investigator-initiated grant from Janssen-Cilag for the PoET Study. MB is supported by a NHMRC Senior Principal Research Fellowship and Leadership 3 Investigator grant (1,156,072 and 2,017,131). P.B. has received speaker fees from Servier and Janssen, educational support from Servier and Lundbeck, is on an advisory board for Incite Health, has been a consultant for Servier, inhaleRx and Greenhorn industries, and has served as DSMC Chair for Douglas Pharmaceuticals.

FUNDING INFORMATION

The PoET study and U.L.'s position is funded by an investigator-initiated grant from Janssen Australia (ACTRN12623001068651 NSLHD); however, the authors received no funding for writing this article.

CONFLICT OF INTEREST STATEMENT

The authors G.S.M., U.L. and E.B. are co-investigators in the PoET Study, Clinical Trial Number: ACTRN12623001068651. The funders have had no input into the writing of this article.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Gin S. Malhi https://orcid.org/0000-0002-4524-9091
Erica Bell https://orcid.org/0000-0002-8483-8497
Uyen Le https://orcid.org/0009-0001-5276-6943
Philip Boyce https://orcid.org/0000-0002-9816-7356
Michael Berk https://orcid.org/0000-0002-5554-6946

ENDNOTE

[i]CADE Clinic, Royal North Shore Hospital: https://www.cadeclinic.com/.

REFERENCES

1. Malhi GS, Bell E, Bassett D, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Australian & New Zealand Journal of Psychiatry*. 2021;55(1):7-117.
2. Sakurai H, Noma H, Watanabe K, Uchida H, Furukawa TA. Cumulative remission rate after sequential treatments in depression: reappraisal of the STAR*D trial data. *World Psychiatry*. 2024;23(1):156-157.
3. Harris MG, Kazdin AE, Chiu WT, et al. Findings from world mental health surveys of the perceived helpfulness of treatment for patients with major depressive disorder. *JAMA Psychiatry*. 2020;77(8):830-841.
4. NICE. *Depression in Adults: Treatment and Management*. Vol NICE Guideline No. NG222. London, UK: National Institute for Health Care Excellence 2022.
5. Strandberg P, Nordenskjöld A, Bodén R, Ekman CJ, Lundberg J, Popiolek K. Electroconvulsive therapy versus repetitive transcranial magnetic stimulation in patients with a depressive episode: a register-based study. *J ECT*. 2024;40(2):88-95. doi:10.1097/YCT.0000000000000971

How to cite this article: Malhi GS, Bell E, Le U, Boyce P, Berk M. Treatment resistant but not irremediable. *Bipolar Disord*. 2024;00:1-4. doi:10.1111/bdi.13490