BJPsych | The British Journal of Psychiatry (2016)
208, 101–103. doi: 10.1192/bjp.bp.115.176479

Editorial

Antidepressant treatment response: 'I want it all, and I want it now!'†

Gin S. Malhi, Anne R. Lingford-Hughes and Allan H. Young

Summary
The treatment of depression remains suboptimal, highlighting the need for more effective antidepressants. Traditional drug discovery and development is time-consuming and costly, prompting the need for faster translation of novel therapies into practice. But clinical expediency comes at a cost against which potential benefits need to be considered judiciously.

Declaration of interest
G.M. reports grants from the National Health and Medical Research Council (NHMRC), Ramsay Research and Teaching Fund, the American Foundation for Suicide Prevention, and personal fees from AstraZeneca, Lundbeck, Janssen, Servier and Elsevier, outside the submitted work. A.R.L-H. reports grants from MRC, Imanova and NIHR RfPB & HTA; grants, personal fees and non-financial support from Lundbeck, and non-financial support from GSK, outside the submitted work. A.H.Y. reports grants from NIMH (USA), CIHR (Canada), NARSAD (USA), Stanley Medical Research Institute (USA), MRC (UK), Wellcome Trust (UK), Royal College of Physicians (Edin), BMA (UK), UBC-VGH Foundation (Canada), WEDC (Canada), CCS Depression Research Fund (Canada), MSFHR (Canada), and NIHR (UK), and investigator-initiated funding from Astra Zeneca, Eli Lilly, Lundbeck and Wyeth, and personal fees from all major pharmaceutical companies with drugs used in affective disorders, outside the submitted work.

Professor Gin S. Malhi (pictured) is Head of the Department of Psychiatry at the University of Sydney and Associate Director of the Kolling Institute. He is also Editor in Chief of the Australian and New Zealand Journal of Psychiatry (ANZJP) and Clinical and Research Director of the CADE Clinic at Royal North Shore Hospital where he pursues his interest in mood disorders. Professor Anne Lingford-Hughes is Professor of Addiction Biology at Imperial College London where she is Deputy-Director of the Centre for Neuropsychopharmacology. She is also Consultant Psychiatrist at Central North West London NHS Foundation Trust where she has particular interest in pharmacological treatment of alcoholism and its comorbidities. Professor Allan Young holds the Chair of Mood Disorders at King's College London where he is also Director of the Centre for Affective Disorders within the Department of Psychological Medicine in the Institute of Psychiatry, Psychology and Neuroscience.

Evaluating antidepressant response

The 'royal' edict from Queen – 'I want it all and I want it now!' – aptly applies to the treatment of major depressive disorder, which will soon be the leading cause of disability worldwide. To achieve remission it typically takes two to three trials of antidepressant treatments and even then only 60–70% of patients reach this goal.[1,2] Furthermore, better tolerability of newer antidepressants has meant that they are prescribed to a wider population of patients, often with fewer depressive symptoms, resulting in poorer response rates.[3] In clinical trials, where antidepressant response is tested more formally, the key problem is that participants are very different to real-world depressed patients. For example, trial patients have fewer comorbidities and less severe illness and consequently, they are generally more homogeneous phenotypically and more responsive to placebo.[4] These discrepancies between actual practice and research trials mean that the response to antidepressants in clinical practice is capricious and usually suboptimal, increasing the urgency and need for more effective and targeted treatments.

Antidepressant efficacy is greatest early in the course of major depressive disorder and more likely when treating depression of mild to moderate severity. In other words, depression that presents to, and is typically managed by, primary care physicians. But general practitioners are already spoilt for choice with respect to the number of antidepressants at their disposal and it is increasingly difficult to demonstrate meaningful benefit of antidepressants over placebo, let alone efficacy of one effective antidepressant over another.[5] Therefore the focus of clinical trials has shifted to testing the efficacy of new medications in patients who have failed to respond to first-line antidepressants. Studies of experimental therapies are now usually initially conducted in patients with treatment-resistant depression using an open-label design and without a placebo control. These compromises are justified because well-designed clinical trials are expensive, and high-risk and necessary large-scale studies are only tractable once there is a reasonable likelihood of success and that can only be gauged by conducting exploratory studies in which neither the design, nor the patient group, is ideal.

Exploring alternative strategies

Based on knowledge of underlying mechanisms, clinicians also conduct preliminary studies with off-label use of medications, albeit on a smaller scale. Hence, robust evidence from clinical trials often lags behind clinical experience. This alternative path to knowledge is defensible provided the process does not halt after the initial step of empirical exploration is completed and is followed by more substantive randomised controlled trials (RCTs) that demonstrate a useful effect. In reality, the latter are increasingly costly and require navigation through many regulatory stipulations that consume months and years, delaying the introduction of potentially effective new treatments to the clinic. Although safety concerns are of course important and efficacy needs to be demonstrated scientifically, the obstacles this process creates has stifled many promising therapies. In the UK this has prompted the government to consider the Medical

†See pp. 108–113, this issue.

https://doi.org/10.1192/bjp.bp.115.176479 Published online by Cambridge University Press

Innovation Bill – colloquially referred to as the Saatchi Bill – that makes provisions for innovation in medical treatment. Specifically, it allows doctors to depart from existing accepted medical treatments provided this is done in a responsible manner and satisfies certain requirements. The Bill has sparked intense debate, especially in the context of cancer therapy, as to the benefits of allowing doctors to expedite the introduction of treatments into clinical practice. Even though its aim of yielding new and novel effective treatments was applauded, many learned organisations felt that use of innovative treatments was not being stifled and that instead research providing an evidence base could be jeopardised by the new Bill. Indeed, much attention was given to the argument that such a development would put patients' well-being and lives in peril from unregulated medical practice. To address the lack of innovation, many suggested that a more productive avenue would be to transform the challenges surrounding research funding and running clinical trials such as the time-consuming and convoluted bureaucracy. Whatever the outcome, we operate in a system where medications take years to develop and may never come to fruition because of huge costs, particularly in disease areas such as psychiatry.

Combating treatment resistance

Treatment-resistant depression and its associated sequelae, namely loss of psychosocial function and risk of suicide, is the psychiatric equivalent in which the imperative to introduce more effective and efficient treatment has to be balanced against demonstrable clinical benefits. Previously, psychosurgery and electroconvulsive therapy have been subject to scrutiny through this bifocal lens. A contemporary exemplar is that of ketamine (see study in this issue of the *BJPsych* by Schoevers and colleagues),[6] which has emerged as a potential treatment for treatment-resistant major depressive disorder on the basis of relatively modest data that are indicative at best and clearly requires further investigation.

For many years ketamine has been used as an analgesic and anaesthetic but it is also a substance of misuse that can produce dissociative and hallucinatory experiences. Thus far its clinical use in the treatment of major depressive disorder has been off-label,[7] and testing of its efficacy in this context began with open-label trials in individuals that had failed available treatment strategies.[8] Gradually, growing enthusiasm has spurred interest for more robust trials and now some are underway.[9] But at the same time, ketamine use has prematurely migrated from treatment-resistant depression to less severe major depressive disorder, a transition accelerated by the fact that a growing number of patients do not fully respond to conventional antidepressants and that functional recovery procured by antidepressant treatment is often incomplete and/or transient.

The process of proving the usefulness of ketamine illustrates many of the difficulties faced by researchers attempting to introduce new treatments into practice. The current drive for psychiatric research and indeed medicine as a whole to be increasingly translational, coupled with the fact that many clinicians feel that it is unethical to make severely depressed patients wait for a treatment to become formally approved, especially when they run the risk of suicide,[10] means that agents such as ketamine will be subject to early adoption into clinical practice via sometimes unorthodox channels.

In the context of major depressive disorder and treatment-resistant depression, the attraction of ketamine is that its mechanism of action is novel and very different to that of conventional antidepressants. Ketamine acts on the glutamatergic neurotransmitter system, engaging *N*-methyl-D-aspartate (NMDA) receptors, rather than directly affecting monoamine neurotransmitters, the main target of conventional antidepressants.[11] The literature thus far suggests that ketamine has an immediate short-lived effect on some symptoms of depression and that this provides transient relief.[12] However, whether this is sustainable without long-term ongoing therapy remains unknown. Furthermore, whether this is a true antidepressant effect, in the conventional sense, or simply an anaesthetic effect needs to be elucidated. In addition, ketamine does have the potential for significant side-effects and these need to be quantified.[13,14] If ketamine is found to have a meaningful 'antidepressant' effect, then the optimal frequency and route of administration also need to be carefully determined and both the short- and long-term risks and benefits need to be comprehensively evaluated. The problem is that definitive answers to these questions will take years of research, whereas in reality, because ketamine is presently available, it is already being administered to patients with depression despite an absence of substantive evidence.

This highlights the problem of reporting preliminary and somewhat tentative research findings as promising or potentially effective and the difficulty of limiting a finding to a specific subpopulation/subtype of major depressive disorder, such as treatment-resistant depression. In practice, such limit-setting is often ineffective and seldom adhered to, and 'research-only' use of medications very quickly becomes generalised, with experimental therapies migrating rapidly across both a wider efficacy profile and a broader patient population. Unfortunately, 'promising findings' are translated as 'some efficacy' and 'patients in whom alternative therapies have failed' is taken to mean 'any non-response'. Eventually, these well-intentioned but poorly defined specifiers can be construed as 'any patients who may not respond', effectively advancing new treatments to the frontline alongside first-line strategies.

Bypassing the usual processes of drug development, which involve stringent checks and balances for evaluating medications prior to their widespread use in clinical practice, means that 'testing' will still occur but in a more unregulated fashion as patients in the general population are exposed to the new medication. In the case of an effective and safe antidepressant treatment this approach may well save time and expedite its delivery to patients. But in cases where a medication is ineffective or has considerable side-effects these problems will take much longer to be observed and may in fact cause significant harm before coming to light.

Conclusions

In summary, the treatment of major depressive disorder remains a serious challenge. It is an illness that affects a growing proportion of our society and yet treatment has not significantly improved in recent decades. Thus there is an understandable desire for new and more effective therapies. However, the current system of developing new medications is slow, protracted and seemingly wasteful and dismissive of innovation. This has meant that new antidepressant treatments often find *ad hoc* pathways into practice via routes that rely on clinical experimentation. This often involves circumventing safety testing and placing greater reliance on softer markers of efficacy, both of which are associated with significant risks. The need for newer, better and faster treatments for the management of depression and its comorbidities is self-evident. Pursuing this goal by dispensing with traditional research methods also comes with significant new costs. Thus, 'wanting everything and wanting it now' is all well and good, but newer and novel treatments are not necessarily better, especially if they are ultimately ineffective and instead cause serious side-effects.

https://doi.org/10.1192/bjp.bp.115.176479 Published online by Cambridge University Press

Gin S. Malhi, Professor and Chair of Psychiatry, and Associate Director Kolling Institute, University of Sydney, Australia; **Anne R. Lingford-Hughes**, Professor of Addiction Biology, Centre for Neuropsychopharmacology, Division of Brain Sciences, Department of Medicine, Imperial College London, UK; **Allan H. Young**, Chair of Mood Disorders and Director of Centre for Affective Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK.

Correspondence: Professor Gin S. Malhi, Department of Psychiatry, University of Sydney CADE Clinic, Level 3, Main Building, Royal North Shore Hospital, St Leonards, Sydney, NSW 2065, Australia. Email: gin.malhi@sydney.edu.au

First received 1 Dec 2015, accepted 8 Dec 2015

References

1 Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *Am J Psychiatry* 2006; **163**: 1905–17.

2 Nierenberg AA, Katz J, Fava M. A critical overview of the pharmacologic management of treatment-resistant depression. *Psychiatr Clin N Am* 2007; **30**: 13–29.

3 Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 2006; **163**: 28–40.

4 Benedetti F. *Placebo Effects: Understanding the Mechanism in Health and Disease*. Oxford University Press, 2009.

5 Malhi GS, Basset D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for management of mood disorders. *Aus NZ J Psychiatry*; 2015: **49**: 1087–1206.

6 Schoevers RA, Chaves TV, Balukova SM, aan het Rot M, Kortekaas R. Oral ketamine for the treatment of pain and treatment-resistant depression. *Br J Psychiatry* 2016; **208**: 108–13.

7 Nguyen L, Marshalek, PJ, Weaver CB, Cramer KJ, Scott EP, Matsumoto RR. Off-label use of transmucosal ketamine as a rapid-acting antidepressant: a retrospective chart review. *Neuropsychiatr Dis Treat* 2015; **11**: 2667–73.

8 DeWilde KE, Levitch CF, Murrough JW, Mathew SJ, Iosifescu DV. The promise of ketamine for treatment-resistant depression: current evidence and future directions. *Ann N Y Acad Sci* 2015; **1345**: 47–58.

9 McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW. A systematic review of meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. *Psychol Med* 2015; **45**: 693–704.

10 Kirby T. Ketamine for depression: the highs and lows. *Lancet Psychiatry* 2015; **2**: 783–4.

11 Newport DJ, Carpenter LL, McDonald WM, Potash JB, Tohen M, Nemeroff CB. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. *Am J Psychiatry Online* 2015; **172**: 950–66.

12 Rasmussen KG. Has psychiatry tamed the 'ketamine tiger'? Considerations on its use for depression and anxiety. *Neuro-Psychopharmacol Biol Psychiatry* 2016; **64**: 218–24.

13 Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusion in treatment-resistant major depression. *Biol Psychiatry* 2013; **74**: 250–6.

14 Murrough JW, Burdick KE, Levitch CF, Perez AM, Brallier JW, Chang LC, et al. Neurocognitive effects of ketamine and association with antidepressant response in individuals with treatment-resistant depression: a randomized controlled trial. *Neuropsychopharmacology* 2015; **40**: 1084–90.

psychiatry in history

A hospital for the mentally ill in the Middle Ages

Fernando Espí Forcén

The Hospital de Folls de Santa María dels Pobres Innocents (Hospital for the Mad of Saint Mary of the Poor Innocents) was founded by Father Joan Gilabert Jofre in May 1409 and opened in June 1410 with the financial support of Lorenzo Saloni and the approval of King Martin I of Aragon and Pope Benedictinus XIII. At that time, 'innocents' was a term used to describe children, people with intellectual disability and people with severe mental illness.

The hospital was conceived as a safe place for people with mental illness. Months before its foundation, Father Jofre had publicly preached against the irrational persecution of the mentally ill and in favour of creation of a special hospital, having seen how both mentally ill men and women were physically and sexually abused and left freezing and starving in the streets. Through the centuries the hospital advocated for the mentally ill and became a pioneer in occupational therapy: men carried out activities in agriculture and women in sewing and knitting. The hospital also became a shelter for orphaned children who lived in the streets. After severe damage by fire in 1547 the building was reconstructed and went through several restorations over the centuries. Since 1963 it has housed the Valencia Public Library.

The gate of the hospital's main entrance from the original 1409 structure has surprisingly survived through the centuries. In the image we can see a characteristic Gothic framed pointed arch with two responds on the sides congruent with the characteristic architectural style in Valencia during the early 15th century. The former tympanum contains today a sculpture of Saint Mary of the Innocents holding baby Jesus.

It is believed that Father Jofre found inspiration in the way mentally ill people received care at the Maristan of Sidi Frej in Fez, Morocco, as he had taken several trips to Muslim territories and was probably exposed to the way mentally ill people received care in the Islamic world. Following the opening of the hospital in Valencia, a similar hospital was founded a few years later in Saragossa, Spain. It was praised by Philippe Pinel at the time of the foundation of moral treatment.

At a time in which a religious approach was often taken to explain mental illness, the Hospital of Valencia is proof of early advocacy and treatment for the mentally ill in the Middle Ages.

Published with the kind permission of Carlos Espi Forcén.

The British Journal of Psychiatry (2016) 208, 103. doi: 10.1192/bjp.bp.115.166108