BJPsych The British Journal of Psychiatry (2026)
229, 1, 108–110. doi: 10.1192/bjp.2025.10521

Letter

Targeting best bets for psychiatric research: lessons from oncology

Michael Berk, Elizabeth D. Williams and Niall Boyce

Keywords
Bipolar type I or II disorder; out-patient treatment; depressive disorders; antipsychotics; psychotic disorders/schizophrenia.

Copyright and usage
© The Author(s), 2025. Published by Cambridge University Press on behalf of Royal College of Psychiatrists.

Unlocking the fundamental pathophysiology of psychiatric disorders, let alone leveraging this knowledge to produce new and better treatments, has been complicated and at times frustrating. Although progress has been made, it has been sporadic and patchy. Many of the major breakthroughs in our understanding of the pathophysiology of the major psychiatric disorders were reverse engineered from the effects of serendipitously discovered agents many decades ago. Many novel technologies such as neuroimaging and genetics promised much and have delivered less than was hoped. We are at an impasse. Even if one does not accept the perspective that biologically based psychiatry is a fundamentally flawed concept, it is sometimes tempting to see the challenge as insurmountably complex. At this moment, it is helpful to step back and consider the broader picture; to identify specific barriers to progress and look for examples of analogous situations in other areas of healthcare, such as oncology, where advances have been made in the face of seemingly insurmountable challenges.

The barriers to progress are legion. The dream of identifying singular molecular pivot points for mental health problems is long dead. Rather, a characteristic of the field is that very large numbers of neurobiological elements or biomarkers seem to be involved, each with small effect and usually reflecting quite divergent yet interacting systems. Intuitively, this calls for systems biology approaches to study neurobiology rather than a focus on single targets.[1] Clinically, disorders are catalogued using phenomenology-based nomenclatures. Some champion the utility of such systems, whereas others are more critical. What both groups agree on is that these diagnoses poorly reflect underlying neurobiology, if they do so at all. Depression is as likely to reflect a singular biology as is cough or abdominal pain. It's a hoary cliché that our disorders are hugely heterogenous and massively overlapping. It is widely acknowledged that the DSM is flawed, yet nobody has come up with a better system – if, by 'better', we mean one that is both clinically pragmatic and facilitates scientific advances. Indeed, it could be argued that systems such as the Research Domain Criteria project, with its preclinical focus, have promised greatly and thus far delivered little, while remaining obscure to working clinicians.

Scientists, meanwhile, can feel as if they are caught in a loop, with every new discovery returning them to the starting point: the knowledge that the brain is the most complex known system, posing seemingly intractable problems to reductionistic approaches. Accessing neural tissue at a granular enough level to understand neurochemistry and neurobiology has massive technical and ethical challenges. Animal models are generously described as imperfect proxies of mental health. Given these manifold issues (and many more), where, if anywhere, do we go from here? One option is to look at successes in other fields and explore relevant lessons. Of course, no medical field is completely analogous with another, and we need to be aware of differences as well as similarities. However, we might ask whether the challenges mental health science faces are quite as unique, or as uniquely difficult, as we imagine – and, if they are not, what we might learn from others.

Cancer is probably the best resourced medical research discipline and one in which spectacular successes are being made in understanding the underlying biology and deriving consequent therapeutics. Data-driven diagnoses and an understanding of the cells of disease origin have enabled identification of molecular subtypes within cancers and development of molecularly targeted therapies. One of the most significant hurdles in treating cancer is tumour heterogeneity. Previous generations spoke of cancers of organs such as the lung and liver. Modern oncology recognises large histological and genetic variations among superficially similar cancers, such as breast adenocarcinoma. Another historical misconception was that such a tumour is an unvarying mass of clonal cancer cells. In fact, most solid tumours are a mosaic of diverse cell populations with their own unique set of genetic mutations, receptor expressions and other characteristics. This internal and ever-evolving diversity is a major driver of treatment resistance. A chemotherapy that eliminates one subpopulation of cancer cells may leave another more resilient subpopulation to proliferate, leading to a recurrence of the disease and a lethal phenotype.

Further complicating matters is the tumour microenvironment. Cancer cells exist within a complex ecosystem of non-cancerous cells, blood vessels and extracellular matrix. This environment can protect them from the body's immune system and from the effects of chemotherapy and radiotherapy. For example, some cells within the microenvironment can release signals that suppress the immune response, whereas others can form a dense physical barrier that prevents drugs from reaching the tumour. The timing of diagnosis is another critical factor. Cancers that are evident in superficial tissues such as breast and skin are easier to diagnose early than those in deep organs, such as pancreatic, ovarian and some lung cancers, which often present with vague or no symptoms in their early stages. This 'silent' growth means that by the time a person feels unwell and seeks medical attention, the cancer has often reached an advanced stage. The lack of effective early screening methods for many of these deep cancers exacerbates this problem, often resulting in entrenched and widespread disease and poor clinical outcomes. The problem of deep cancers is not confined to timely recognition by the sufferer. It is technically easier to image, biopsy and perform surgery on superficial than deep organ tumours. It is also much easier to manage early-stage compared with late-stage cancer.

Yet there are key factors that cancer research has been able to turn to its advantage, leading to better understanding, prevention and treatment, and extending and improving the quality of countless lives worldwide. These include the physical presence of a tumour, standing in stark contrast to the more abstract presentations of most mental health conditions; whatever the complex systemic manifestations of a malignancy, there is usually

https://doi.org/10.1192/bjp.2025.10521 Published online by Cambridge University Press

an identifiable primary lesion. Cancer research has also at times had the advantage of being able to identify a relatively small number of risk factors of large effect – such as smoking for lung and bladder cancers, and solar insolation for melanoma. This facilitates understanding of the intersection with pathophysiology.

Furthermore, the cancer field has invested most heavily in conditions such as breast cancer that share enablers of easier success. It has serially targeted identifiable cancer subtypes, such as oestrogen receptor-positive and HER2-positive breast cancers, which has led to treatments targeting these receptors that significantly improve survival. Furthermore, although HER2-targeted therapies were originally developed for breast cancer, they are now being used in subsets of several non-breast solid tumours (e.g. gastric, colorectal, biliary tract and non-small-cell lung cancers) owing to the discovery of HER2 overexpression, amplification or mutations in these cancers. Importantly, these subtypes can be identified via assays that are routinely performed in pathology laboratories. Success in these selected subtypes has built the first bridge, which the field has traversed to reach subsequent adjacent targets. In other words, the field picked winners, and, learning from these, moved serially to other subtypes and challenges. Rheumatology and neurology also have examples of complex conditions initially described by symptoms and syndromes but later refined by biological findings, allowing for the gradual accretion of targeted treatments.

So, what can psychiatry learn from oncology? Reiterating and acknowledging the caveat that there are major differences between mental health and cancer, and that not all extrapolations are feasible or appropriate, let's begin with heterogeneity and subtyping. Few would believe that our current nosology has come anywhere near cleaving nature at its joints. Phenomenology, although a valuable method to identify salient features of mental health problems and perhaps discover key dimensions neglected by the diagnostic manual-driven approach, has limitations in terms of defining subtypes that have been extensively debated elsewhere. What can be termed top-down biomarkers – such as imaging findings, peripheral blood markers or others – have failed to date to differentiate major disorder or find coherent subgroups with sensitivity or specificity that is clinically useful.[2] But we may have neglected what could be termed bottom-up biomarkers. In this context, we can define a bottom-up biomarker as one which by dint of a measurable characteristic defines distinct subgroups.

For the purpose of this argument, we propose that the most neglected and promising bottom-up biomarker is excellent treatment response. Individuals whose conditions show exceptional responses to treatment have been studied in the setting of cancer, and in some cases specific molecular traits have been associated with these responses. The impact of these discoveries has been limited by the small number of people enrolled in these studies, and it is likely that integrated global efforts will be required to drive further breakthroughs.[3]

In the context of psychiatric illness, one example is that lithium has a narrow efficacy profile in bipolar disorder, with only a suggestion of value in a subtype of highly recurrent unipolar depression. One could look at people with catatonia, obsessive–compulsive disorder (OCD), depression or schizophrenia whose conditions are highly responsive to treatment; however, the dichotomising capacity is weaker in psychiatry than in oncology because of a couple of factors. First, excellent lithium response, when it occurs is truly life-transforming and obvious at a distance. In this context, the use of the term response is probably more aligned with the notion of recovery (i.e. sustained symptom resolution, reduced recurrences and restored functional capacity). The issue of placebo response is an obvious confounder. This is to some extent mitigated by use of measures such as the Alda scale, which takes a life course approach rather than looking at change in an index episode. Response over time is much more likely to provide a true index of response, because placebo responses tend to be fleeting.

Although it is clear that many people with diverse disorders can have an outstanding response to treatment, the threshold for response in depression is more on a continuum, with 50% reduction normally being regarded as response; similarly, response in schizophrenia is often defined as a 20% reduction on a measure such as the Positive and Negative Syndrome Scale. The other complexity with antidepressants and antipsychotics is their putative utility across a much wider spectrum of disorders, making them far less of a precision tool. In a sprint race to pick a winner, lithium probably wins this one by a nose.

The obvious attraction of a treatment response biomarker is that by implication it successfully targets the biology of the index disorder. In this regard, lithium is one of few agents in psychiatry that is clearly disease modifying.[4] This is true for its potential to prevent both progression of the primary psychiatric disorder (neuroprogression) and that of commonly comorbid somatic disorders (somatoprogression).[5] If we follow our breast cancer subtype analogy, it makes sense to reduce heterogeneity as far as possible, by focusing on only very clear and dramatic responses, and on people with very narrowly defined illnesses, such as clear non-comorbid and florid euphoric mania. Again, the bridge analogy applies. The chances of success in understanding neurobiology and pathophysiology are highest in the most narrowly defined and homogenous group. And success here provides a route to the next subtype, the identity of which may be implied by discoveries in the initial phase of the work.

In parallel, it makes sense to prioritise disorders that are the most homogenous, inasmuch as anything can be said to be homogenous in psychiatry. Mania only occurs in bipolar disorder, notwithstanding spectral overlap with disorders such as schizophrenia. OCD is also a fairly tight and discrete phenotype. By contrast, depression is a biological tower of Babel, and many have argued that schizophrenia is best described using the plural, schizophrenias. It is hard to think of a disorder in which anxiety is not present, and low mood is equally ubiquitous in an array of disorders that cause distress. This is not to negate the importance, burden and prevalence of these disorders; rather it is about picking the most proximal and feasible target for prioritisation for which wins are likely and where we might learn valuable lessons to apply to more challenging areas. If one was to study a highly heterogenous disorder like depression, it would make sense to focus on seemingly discrete subtypes. Atypical depression, melancholia, the cognitive biotype and the construct of immunometabolic depression are other examples, with the caveat that these currently have unclear and permeable boundaries.

Following this line of argument, it makes sense in studies attempting to understand neurobiology and pathophysiology to exclude people with significant psychiatric or medical comorbidity. Although this comes at a cost to feasibility and hence resource requirements, the homogeneity of the sample may allow smaller samples if the approach provides a greater signal-to-noise ratio than expected. The other cost is generalisability, but the bridge analogy applies here as well. We need to pick our initial targets with care and focus if we are ultimately to benefit all. It also makes sense to target disorders where symptoms track to putative biological pathways. For example, we have a good understanding of the circuits involved in OCD, and the mitochondrial hypothesis of bipolar disorder posits that it is a bioenergetic dysregulation. In mania, there is excessive energy generation unlinked to environmental demands, and in depression there is inability to generate energy in response to demand. This implicates a molecular toggle

https://doi.org/10.1192/bjp.2025.10521 Published online by Cambridge University Press

switch between depression and mania, and mitochondrial regulators have high face validity in this regard. These are known, narrowing the required research focus.[6]

To return to the systems biology construct mentioned above, given the array of biological pathways involved, it makes sense to prioritise methodological approaches that capture this complexity and analytic approaches suited thereto. Omics technologies are maturing, including transcriptomics, lipidomics and proteomics. Adaptation of these approaches to liquid biopsies is critical for developing tools that can contribute to the molecular description of psychiatric disorders and monitoring of treatment responses. In addition, big data and machine learning analytic approaches have potential as novel methodologies for dealing with multivariate data-sets.

Detecting early-stage cancer is critical; many types including breast cancer, bowel cancer and melanoma have excellent prognosis if detected and treated before they have spread. It is intuitively appealing to follow this in psychiatry. There is some evidence that early treatment of disorders including bipolar disorder with agents such as lithium is associated with better prognosis.[7] The same is likely to be true of schizophrenia, although the data for depression are far less clear. There is also some, albeit emerging, evidence that there are biological processes that are disorder specific and some that are linked to the neuroprogression of the index disorders, albeit again with some fuzziness and overlap in boundaries. For this reason, it probably makes sense to focus on earlier-stage disorders. This is particularly true in the setting of disease-modifying therapies, where the ultimate goal is to change the trajectory of the illness and improve long-term outcomes. Last, excellent treatment response could be a powerful tool for successful transdiagnostic research, given that several treatments have cross-diagnostic utility.

As a parallel with the importance of the tumour microenvironment, it will be critical to precisely and comprehensively account for the psychiatric exposome. There is a plethora of social environmental and lifestyle variables that impinge on the risk for and course of mental illness. A biologically informed approach to mental health does not deny these but embraces them. Although selection strategies and inclusion criteria will need to prioritise homogeneity, it needs to be acknowledged that a bewildering array of factors influence psychiatric disorders, and, as far as possible, these need to be identified, measured and adjusted for. Ultimately, a patient-centric precision medicine approach, like that applied to cancer, that is molecularly informed and incorporates identification of the most germane outcomes together with information about the individual person and their specific illness holds promise for moving away from cookie-cutter one-size-fits-all treatments to the personalised right treatment at the right time at the right dose.

Discovery resourcing remains critical. Investment in global mental health research has been estimated at US$3.7 billion per year (2015–2019), with just over half (56%) addressing fundamental research and aetiology.[8] By contrast, investment in cancer research averaged US$4.9 billion over a similar period (2016–2020), of which 73.5% was for blue-sky preclinical research (typically laboratory studies).[9] Thus, a significant proportion of funding goes towards understanding cancer's fundamental mechanisms and enables innovation to flourish. These investigations are critical to enable a deep and nuanced understanding that results in identification of underlying causes and possible therapeutic targets, which in turn drives the development of potential new therapeutic interventions. Fortunately, we can leverage the investments made in well-funded fields such as cancer and repurpose technological, methodological and conceptual developments to advance psychiatric research. Facilitating cross-pollination across seemingly disparate disciplines is one way to drive such progress.

So, if we look at these circles on the Venn diagram, where do they coalesce? People with classical bipolar I mania that is highly responsive to lithium would seem to be a prototype best bet for priority focus, probably at the early stage. Ultimately, we should aim to identify 'winning bets' within major clinical domains of psychiatry: finding a robust marker or characteristic (e.g. excellent response to a particular treatment) across specific patient subgroups (bipolar disorder, psychosis, OCD, etc.). The challenge of cracking the neurobiology of psychiatric disorders is tough enough. We argue that some cracks already exist. Perhaps we need to go where the shard of light is shining through.

Michael Berk, MBBCh, MMed(Psych), FF(Psych)SA, PhD, FRANZCP, FAAHMS, FAASA, Institute for Mental and Physical Health and Clinical Translation (IMPACT), School of Medicine, Deakin University, Barwon Health, Geelong, Victoria, Australia; Orygen, National Centre of Excellence in Youth Mental Health, and the Centre for Youth Mental Health, Melbourne, Victoria, Australia; Florey Institute for Neuroscience and Mental Health, Melbourne, Victoria, Australia; Department of Psychiatry, University of Melbourne, Victoria, Australia; and School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; **Elizabeth D. Williams**, BSc(Hons), PhD, FFSc (RCPA), Institute for Mental and Physical Health and Clinical Translation (IMPACT), School of Medicine, Deakin University, Geelong, Victoria, Australia; and Centre for Genomics and Personalised Health, School of Biomedical Sciences, Queensland University of Technology (QUT), Brisbane, Queensland, Australia; **Niall Boyce**, MBBS, MA, PhD, MRCPsych, Mental Health, Wellcome, London, UK

Correspondence: Michael Berk. Email: michael.berk@deakin.edu.au

First received 2 Sep 2025, final revision 19 Nov 2025, accepted 21 Nov 2025

Author contributions

M.B. generated the first draft of the manuscript, to which E.D.W. and N.B. made substantive contributions. All authors viewed and approved the final manuscript. The views expressed here are those of individual authors and do not necessarily reflect those of their institutions.

Funding

M.B. is supported by a National Health and Medical Research Council Leadership 3 Investigator grant (GNT2017131).

Declaration of interest

M.B. has received grant funding from the Wellcome Trust, Medical Research Future Fund, Victorian Government Department of Jobs, Precincts and Regions, Janssen Lundbeckfonden Copenhagen, St. Biopharma, Milken Baszucki Brain Research Fund, Stanley Medical Research Institute, Danmarks Frie Forskningsfond Psykiatrisk Center Kovenhavn, Patient-Centered Outcomes Research Institute, Australian Eating Disorders Research and Translation Centre, USA Department of Defense Office of the Congressionally Directed Medical Research Programs, Equity Trustees Limited; and has served on advisory boards for Janssen, Otsuka, St Biopharma, Actinogen and Servier – all unrelated to this work.

References

1 Öngür D. Focusing on the biological system instead of the biological level in psychiatry research. *Harvard Rev Psychiatry* 2019; **27**: 333–5.

2 Berk M. Biomarkers in psychiatric disorders: status quo, impediments and facilitators. *World Psychiatry* 2023; **22**: 174.

3 Conley BA, Staudt L, Takebe N, Wheeler DA, Wang L, Cardenas MF, et al. The exceptional responders initiative: feasibility of a National Cancer Institute pilot study. *JNCI* 2021; **113**: 27–37.

4 Post RM, Li VW, Berk M, Yatham LN. Lithium as a disease-modifying drug for bipolar disorder. *Lancet Psychiatry* 2025; **12**: 863–8.

5 Berk M, Forbes M. The parallel roads of neuroprogression and somatoprogression: implications for clinical care. *Am J Geriatr Psychiatry* 2024; **32**: 968.

6 Morris G, Walder K, McGee SL, Dean OM, Tye SJ, Maes M, et al. A model of the mitochondrial basis of bipolar disorder. *Neurosci Biobehav Rev* 2017; **74**: 1–20.

7 Kessing LV, Vradi E, Andersen PK. Starting lithium prophylaxis early v. late in bipolar disorder. *Br J Psychiatry* 2014; **205**: 214–20.

8 Woelbert E, Lundell-Smith K, White R, Kemmer D. Accounting for mental health research funding: developing a quantitative baseline of global investments. *Lancet Psychiatry* 2021; **8**: 250.

9 McIntosh SA, Alam F, Adams L, Boon IS, Callaghan J, Conti I, et al. Global funding for cancer research between 2016 and 2020: a content analysis of public and philanthropic investments. *Lancet Oncol* 2023; **24**: 636.

https://doi.org/10.1192/bjp.2025.10521 Published online by Cambridge University Press