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Lost in translation: toward clinically effective translational research

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Despite the increased access to and variety of psychotropic drugs available for treatment of mood and anxiety disorders, the prevalence of these disorders is still rising, indicating that current treatment approaches are broadly ineffective. We suggest that this inefficacy is due in large part to the current approach to translational research between neuroscience and psychiatry. Animal models aim to replicate, as closely as possible, the symptoms of disorders observed in people. These models are then used to assess genetic susceptibilities and neurophysiological and cellular underpinnings of functional impairments and to search for observable biomarkers and druggable targets. At the same time, clinical work is focused on symptom diagnosis and management, often relying on the same druggable targets that have been fed up the translational chain. This approach has in large part resulted from psychiatry's historical medicalization of mental illness that encourages both basic and clinical researchers to limit the search to treatable biological causes for mood disorders, often based on a single chemical or neurotransmitter explanation. By reviewing results from both animal and patient studies, we show that the methods and diagnostic frameworks employed do not adequately capture either the symptoms of disorders of interest or the effects of drugs measured in animal models, or the development, life course, and trajectory of mood disorders in people. This failure results in a bidirectional self-reinforcing cycle of inefficacy of translational research. We suggest that a focus on the environmental, social and psychological context in which mood disorders arise and are treated is crucial to developing truly translational models and research strategies.

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INTRODUCTION

Mood and anxiety disorders are among the most common mental disorders globally, estimated to affect approximately 500 million people worldwide [1]. The World Health Organization estimated the global prevalence of depression in 2015 to be 4.4%, and anxiety to be 3.6% [1], with surveys indicating that mental disorders result in significant disability [2]. This has resulted in an international focus on resources targeted at increasing available treatment and intervention of mood disorders. Over the years, mental health treatment has become more accessible at all levels of care; there is an increase in mental health services and professionals, and a greater range and availability of psychotropic medication [3].

Generally, when there is an increase in availability and accessibility of appropriate and effective treatment for a disease, the prevalence of that disease reduces [4]. However, since the increased availability and utility of treatment for mental illness, particularly antidepressants, in developing countries, there has been no reduction in the prevalence of mood or anxiety disorders, in fact, trends indicate increases [4]. Ormel et al. coined this phenomenon the "treatment-prevalence paradox" which brings about questions around the quality and not quantity of available treatment. It is likely that prevalence may also reflect broader societal changes, such as increased economic disparity, reduced social cohesion, and chronic stress, which are known to elevate risk for mood and anxiety disorders [5]. However, even when accounting for these contextual factors, the lack of meaningful reduction (and in some places, a rise) in prevalence, despite increased access to treatment raises questions about the underlying assumptions guiding current treatment paradigms.

Explanatory models of mental illness have developed over the years to account for cultural and societal needs – such as the encouraged use of the "chemical imbalance" theory as an explanation for depression in order to reduce self-blame and stigma, and increase adherence and utility of medical intervention [6]. On the other hand, recent studies have demonstrated that although the chemical imbalance explanation did result in reduced self-stigma, it also caused worse expected prognosis, a perception that non-medical interventions were ineffective [7], and poorer self-efficacy [8].

Clinically, a single chemical explanation for the cause of mood disorder is an attractive oversimplification which permits the idea that there is a targeted, precise, and hopeful approach to the search for the right neurochemical treatment. This approach has been termed a "delusion of precision" to describe the limited neurobiological core understanding of psychopharmacology in which clinicians view medical treatment of mental illness to be "precise, concrete, straightforward, and specific" [9]. This simplified approach leads to loss of understanding and accounting for the complex underpinnings of mental health difficulties, which more

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so than physical illness, can be precipitated and perpetuated by psychological components such as thoughts, language, context, and emotions that directly impact the presentation, severity and trajectory of mood and anxiety disorders [10]. In addition, when examining the evidence for a chemical imbalance to explain mood and anxiety disorder, there is a lack of literature indicating a causal relationship between neurotransmitter imbalance and mood difficulties [11, 12].

We suggest that this historical and ongoing reliance on single-chemical explanations for mood disorders is a key determinant of the continued intractability of treatment approaches. Animal research has largely been constrained by these concepts and this has resulted in attempts at translational research that do not accurately reflect mental disorder or treatment utility in people. At the same time, clinical characterization often suffers from a simplistic and medicalized view of disorder which leads to a constrained and narrow understanding of the lived experience of disorder and treatment in patients.

Here we review research from both human and animal studies which suggests that at both the animal and clinical levels, failure to take into account the holistic context and trajectory of mood disorders has hamstrung attempts to develop truly translational models and therefore effective interventions. By highlighting the gaps and interplay between clinical and animal research in both defining and modeling mood and anxiety disorders and the effects of treatment drugs we show that translational research is trapped in a self-perpetuating cycle of inefficacy. We suggest that renewed focus on a more holistic understanding of the determinants and trajectory of mood disorders as well as the overall therapeutic context, including the multifaceted effects of treatment drugs, is critical to both improved treatment outcomes and better animal models with more translational utility.

THE COMPLEXITY OF MENTAL DISORDERS

Understanding models of mental health

Proposed by George Engel in 1977, the biopsychosocial model (BPSM) examines how individuals perceive their environment and how these perceptions influence their health and biological processes [13]. Modern BPSM frameworks explore the interactions between biological, psychological, and social factors to better understand how psychosocial influences shape neurobiology and impact an individual's overall well-being [14].

The transactional nature of mental disorder development can be described as a dynamic and reciprocal process between an individual and their environment, wherein the individual's behaviour and emotional responses shape their environment, and vice versa, influencing their mental health outcomes over time [15].

Transactional models explain reality and lived experience as emerging from the dynamic interplay between individuals and their social and physical environments with research demonstrating that neural plasticity allows the brain to adapt structurally and functionally in response to experiences [16]. For instance, learning a new musical instrument leads to increased grey matter volume in motor and auditory regions, as well as strengthened connectivity between these areas [17]. Similarly, practicing a sport induces neuroplastic changes, such as enhanced motor cortex activation, synaptic efficiency, and coordination-related neural pathways [18]. These findings highlight the brain's capacity for experience-dependent plasticity, reinforcing the idea that environmental stimuli play a critical role in shaping neural architecture and cognitive function.

A person who experiences distress or depression might respond by withdrawing from social situations, which could limit their exposure to enriching, supportive environments. This avoidance, in turn, may reduce opportunities for positive social interactions, reinforcement, or problem-solving experiences that could foster resilience and mental well-being [19]. Repeated withdrawal can create a cycle of isolation, reinforcing negative emotional states and reducing the brain's capacity to adapt to new, positive stimuli [16, 19]. Over time, neuroplastic changes could occur, such as reduced synaptic connections or neurotransmitter dysregulation, leading to a further diminishment of cognitive and emotional flexibility, as seen in disorders like depression [20, 21].

Another example of this can be observed in the development of anxiety disorders, where early environmental stressors, such as traumatic experiences or chronic stress, set the stage for maladaptive responses [22]. Initially, these responses, such as heightened anxiety and avoidance behaviours, may serve a protective function, helping an individual cope with immediate stressors. However, if these behaviours become repetitive and habitual, they limit exposure to new, potentially less stressful experiences, and may even inhibit the development of coping strategies [23]. This withdrawal from challenges and the avoidance of feared situations can result in fewer opportunities for learning and positive reinforcement, reinforcing the cycle of anxiety [22].

Neurobiologically, this cycle of avoidance and anxiety can lead to alterations in brain regions involved in emotional regulation. Chronic anxiety can cause decreased activity in the prefrontal cortex, which is responsible for regulating emotional responses, while increasing activity in the amygdala, the brain's centre for processing fear and threat [24]. Over time, these neurobiological changes can heighten sensitivity to perceived threats, thus perpetuating the individual's anxious thoughts and behaviours. Furthermore, alterations in neurotransmitter systems, such as serotonin and dopamine, can exacerbate symptoms and contribute to the persistence of anxiety [23].

This process illustrates the importance of examining the development and therefore intervention of mental health challenges through a lens that is not limited to biological or genetic predispositions but also from the ongoing, transactional interaction between an individual's neurobiology, behaviour, and their broader environmental context [15, 16, 25].

Are animal models modeling the right things?

Much of what we've learned about the biological and genetic contributions to psychiatric disease has come from animal models [26]. Traditionally, animal models of psychiatric disease, due to the difficulty of modeling the human condition in its entirety, have focused on specific symptoms and tried to model these behaviourally. With the advent of molecular genetic approaches, researchers can also study the impacts of modifications of specific genes on behaviour with relevance to a range of psychiatric conditions–a so-called endophenotype approach [27]. Once a model is found which recapitulates to the extent possible the clinical symptoms of the disorder, researchers search for neurobiological correlates of the behaviour that relates to the symptoms [28]. This information is then fed back up the translational chain into drug development and clinical trials, which then inform clinicians who prescribe medication based on the purported biological targets.

This approach to animal modeling has frequently resulted in a parsing of psychiatric conditions into component parts with specific neurobiological correlates rather than considering the conditions in a wholistic manner as discussed above [28]. While much has been learned using this approach, translational models of diseases, or in this case, disorders, such as depression and anxiety remain elusive [29–31].

If we consider as an example animal models of anxiety, we can see how a piecemeal approach to specific animal behaviours with proposed relevance to the human condition can hamper translational potential. While a number of experimental preparations have been developed [32], use has tended towards tests that are easily set up and run, and that provide a high throughput reading of putative anxiety-related behaviour in order to test

drugs. Most of these assays were developed to test the effects of benzodiazepines on anxiety-relevant behaviour. The most commonly-used tests rely on the conflict between a rodent's natural tendency to explore and the drive to avoid situations that may be dangerous.

For example, the open-field test, which is the most commonly-used test in psychology and neuroscience investigations of animal behaviour, assesses the type of activity a rodent engages in when placed in a large open field [33]. This test is thought to capitalize on the innate conflict between an animal's desire to explore novel environments and the cautionary tendency to avoid potentially-dangerous areas. Rodents, in particular, display an innate fear of open spaces (due to the lack of cover from overhead predators). Thus, animals that are thought to be more anxious in this test will spend less time in the centre of the field and more time hugging the sides or corners [32, 34].

Although this test has been shown to be a sensitive and effective screen of the anxiolytic potential of classical benzodiazepines and 5-HT1a receptor agonists, such as buspirone, it is not sensitive to other compounds which display clinical efficacy in a range of pathological anxiety disorders, including many SSRIs [29]. Thus, the open-field test may be an effective test of anxiety that occurs within the normal range of experience, such as when someone is confronted with a threatening or stressful situation. It does not, however, appear to be sensitive to the type of anxiety-related behaviours that are symptomatic of the suite of DSM-V diagnoses termed anxiety disorders. In their review of open-field studies to that point, Prut and Belzung (2003) cautioned "it is possible we are trapped by the terminology and that the psychiatric diseases termed "anxiety disorders" may have no relationship with anxiety-like behaviour (p 28)" [34, 35].

This disconnect plays out at the clinical level as well, in that when considering normal vs abnormal states, clinicians often place excessive emphasis on the severity and duration of symptoms when determining pathology [36]. Generally, anxiety serves an adaptive function—heightened sensitivity to threats may be advantageous in certain contexts but distressing in others. However, the current diagnostic approach often disregards the situational context in which anxiety arises, treating it as inherently disordered rather than a functional understanding of emotional regulation. This reductionist framework fails to differentiate between anxiety that is functional and protective versus anxiety that is truly maladaptive and impairing [37]. It would be beneficial for clinicians to transition toward a more nuanced, context-sensitive approach that distinguishes between adaptive and maladaptive responses [38].

Many of the other assays in animal models have been subject to the same criticism, and have the same limitations as the open field test, for example the elevated plus maze [39] and the light/dark exploration test [29, 40, 41]. In both tests, the "anxiety" related behaviour is decreased by anxiolytic drugs. There are a number of other assays that purport to index behaviour with relevance to human anxiety states [42]. The vast majority of studies, however, have used a small subset of these tests, including the three discussed above.

This, along with a combination of other factors, such as the majority of tests being conducted on male animals (notwithstanding anxiety diagnoses occurring in women at twice the rate of men), assessing only acute drug effects (despite most treatments being at least semi-chronic), assessing only "normal" anxiety states (rather than pathological syndromes [43]), and focusing on single molecular targets in complex, yet poorly understood neurobiological systems, has led to what Griebel and Holmes (2013) call limited predictive and "postdictive" validity [29].

The lack of predictive validity is evident in that the most clear and reproducible effects on these behavioural paradigms are from benzodiazepines, with much less sensitivity to drugs which target the 5-HT system, including SSRIs. Going from the clinic to the lab also indicates lack of "postdictive" validity, in that these tests are often not sensitive to the effects of a range of other clinically-efficacious anxiety drugs. Thus, notwithstanding their ease of use and high-throughput nature, the most commonly-used tests of anxiety have produced little in the way of transformative translational results. The same can be said for animal models of depression [30, 44–46].

Diagnostic and clinical inconsistency

The difficulty in designing or conceptualizing clinically-applicable animal models is worsened by the state of understanding of significant aspects of clinical diagnoses in the human literature. Attempts at homogenising mood and anxiety disorders, largely based on the medicalization of mental health without consideration of the epidemiological and psychosocial context has resulted in missed understanding of the disorder trajectory and difficulties differentiating between normal and pathological expressions. For example, it is thought that individuals experiencing brief episodes of depression, such as those lasting under two months, with similar recurrence as those with no history of depressive symptoms [47] are more appropriately understood as experiencing normal intense sadness [48]. The same can be said for depressive symptoms occurring within weeks/months after a significant loss as an experience of grief [49]. It would be quite common, however, for individuals who experience such symptoms to be diagnosed as being "depressed" and possibly medicated.

Even if our animal models were better at modelling the broad range of symptoms used to diagnose clinical populations, it is unclear what aspects of the diagnoses are most relevant to model [44, 50]. While relatively easy to use for clinicians, the DSM-5 framework of adding up symptoms and comparing them to thresholds that differentiate between disordered and non-disordered populations does not account for the high heterogeneity within the disorder in clinical populations. For example, a study examining depression symptom profiles of 3703 depressed patients in the STAR*D project, one of the most comprehensive real-world studies of antidepressant treatment, found 1030 unique symptom profiles, with the most common profile only shared by 2% of the participants [51], suggesting that depression could be a collection of distinct but overlapping syndromes. This heterogeneity is also reflected in the neuroscience literature by a failure to identify consistent and replicable biomarkers [52–54]. Further highlighting the complexity of defining depression, Fried (2017) examined seven commonly used depression scales and found substantial variation in the symptoms they assessed. Across these scales, researchers identified 52 distinct symptoms, with significant differences in how each scale conceptualized and measured depression. The mean overlap among the scales was low, again underscoring the heterogeneity of depressive syndrome [55]. Thus, a symptom-based approach, while conceptually accessible, has resulted in little in the way of useful clinical results.

A significant challenge in assessing the efficacy of antidepressant treatment is the high prevalence of spontaneous recovery and placebo effects. In a meta-analysis encompassing 177 studies (44,240 patients), 54% of patients responded to antidepressants, while 38% demonstrated improvement on placebo [56]. Similar patterns have been observed with psychotherapy, where response rates reached 54%, compared to 41% in control conditions [57]. Moreover, individuals experiencing depressive symptoms who do not seek professional treatment often exhibit comparable rates of spontaneous recovery.

To further illustrate this, in a study using "watchful waiting" as an approach, 64.5% of patients who initially sought treatment for depression recovered without the need for treatment (pharmacotherapy or psychotherapy) after a three-month follow-up [58]. Notably, the severity of depression did not predict treatment outcome. This phenomenon complicates both clinical and

research-based assessments of treatment efficacy, as improvements in symptoms may be erroneously attributed to the intervention when, in fact, they may have resolved independently.

These considerations highlight the fact that the core challenge in understanding mental disorders lies in the fact that their precise aetiology remains unknown. As a result, diagnosis and treatment have traditionally been based on symptom presentation rather than underlying mechanisms. There is a clear need to bridge biological and psychological perspectives in mental health research, fostering greater integration between preclinical and clinical approaches to improve both conceptual models and therapeutic strategies.

PSYCHOTROPIC DRUG EFFECTS

Primary vs secondary drug effects

Another contributor to lack of translational efficacy of results from animal models is the insensitivity of many animal-behavioural paradigms to "primary" vs "secondary" drug effects. For example, while animal models of anxiety cannot model all of the primary and secondary effects of clinical drugs due to the inherent subjectivity of the human experience, many studies have been conducted to assess basic behavioural impacts of anxiolytics [29, 59]. Typically, in animal models that assess the impacts of anxiolytic drugs, the primary effect would be a decrease in anxiety-related behaviour (more time spent in the middle of the open field or open arms of a maze), while the secondary effect would be anything else the drug does that is not related to relieving anxiety. For the assessment to have clinical validity, the behavioural paradigm needs to be able to differentiate anxiolytic effects from other effects.

In humans, the main (or primary) effect of a drug is defined as the primary therapeutic outcome for which the drug is prescribed, aimed at addressing the condition or symptoms. In contrast, the side (or secondary) effects of a drug are considered the unintended or secondary consequences that arise from its use, which can either be mild or severe. For example, in benzodiazepines, which are frequently prescribed for anxiety disorders, the main effect of the drug is to produce a calming effect to reduce anxiety through enhancing the activity of gamma-aminobutyric acid (GABA) [60]. However, side effects can include drowsiness, dizziness, memory impairment, and an increased risk of dependence with long-term use [61].

How well do common tests of the anxiolytic properties of benzodiazepines differentiate between primary and secondary effects? In a recent investigation, Pádua-Reis et al (2021) assessed the impact of diazepam (a drug that was synthesized in 1959 and widely used to treat anxiety) on behaviour in an open field and elevated plus maze. Critically, their analysis was able to differentiate the typical indicators of anxiolysis from a more general sedative effect of diazepam. They found that diazepam decreased entry into the open arms in the elevated plus maze (particularly at higher doses) but that it also decreased the overall time spent moving, a sedative effect. In the open field, they found that diazepam dose-dependently decreased overall movement and entries and time in the center, an overall sedative effect. They concluded that their analyses provided no evidence for an anxiolytic effect of diazepam. Rather, their results could be attributed solely to a sedative effect [62, 63].

This result is reflected in clinical literature in a term coined by Breggin (1997) [64] who described the "brain-disabling theory" of psychiatric treatments, which suggests that rather than correcting underlying neurobiological imbalances, psychotropic drugs may induce changes that impair normal brain function [65]. This occurs when effects such as sedation, numbness, and reduced thought processes may mask anxious or depressive processes and be interpreted as a reduction in symptoms, such as with increased sleep and decreased agitation [65].

Qualitative studies also capture the challenges faced by individuals who experience "brain-disabling" and other side effects, such as the impact of sexual dysfunction and emotional numbing on relationships [66, 67], sedation on work tasks [68], and the paradoxical impact of adverse medication effects on overall quality of life [69]. For example, a meta-analysis of current users of benzodiazepines showed statistically significant cognitive impairments in working memory, processing speed, divided attention, visuoconstruction, recent memory, and expressive language [70], suggesting the presence of functional impairments.

Similar results have been found with antidepressants. In the largest survey of antidepressant use to date with a sample of 1829 New Zealanders, participants reported sexual difficulties (62%), emotional numbness (60%), and a sense of not feeling like themselves (52%). Other common adverse effects included agitation (47%), a reduction in positive feelings (42%), suicidality (39%), and caring less about others (39%). These reported side effects were similar to data seen in other international studies [71–73]. Most clinical trials primarily focus on evaluating the intended outcomes of these drugs, often neglecting to fully address the broader and potentially adverse impacts that patients may experience from side effects in daily life, side effects which in some cases can be more disruptive than the initial condition for which the patient sought treatment.

In addition, side effects may also masquerade as psychiatric symptoms. Because the DSM-5 criteria does not take into account the side effects of medication on a patient's presentation, and therefore medication effects such as low energy, reduced participation in activities, difficulties concentrating, impaired cognition, suicidality, change in sleep and appetite may also be mistaken for symptoms of mental disorder.

These considerations highlight the importance of making sure the behavioural tests (and clinical evaluations) that one uses to assess the impacts of therapeutic drugs are fit for purpose. Specifically, for any conclusions about a drug-specific effect to be made, researchers must be able to differentiate primary vs secondary effects and to assess the effects of the drugs in preparations that mimic as closely as possible the range of clinical conditions experienced by humans. The range of secondary effects in need of being incorporated into animal models is ever-growing as the human clinical literature expands and becomes more nuanced.

Lack of long-term studies

Another major factor that makes results from animal studies difficult to translate to the clinic is the fact that many studies of the impacts of drugs used to treat mood disorders do not administer the drugs in a way that is comparable to the way they are used in patients. This becomes particularly problematic when considering that although most studies of administration of drugs used to treat mood disorders in humans focus on acute administration, clinical use of these substances is rarely acute, and in most cases continues for many years [74], with a recent study showing the duration of antidepressant use having doubled in the last 20 years [75, 76]. The gap in the research literature on acute vs long term effects is startling and made even more clear when we realize that even animal studies that claim to study chronic or long-term effects of anxiolytic or antidepressant drugs rarely continue administration past three weeks and most only up to two [77–85] but see Carton et al., 2021 [86] and Kroeze et al., 2015 [87]). Thus, notwithstanding the millions of people who are prescribed and continue to use mood disorder drugs for years [74, 88, 89], there are precious few data from animal models that have looked at analogous timeframes.

Even shorter timeframes, however, have shown multi-pronged adaptive neural responses after use of both benzodiazepines and SSRIs [87, 90]. In terms of antidepressants, most chronic studies are focused on uncovering purportedly adaptive neuroadaptations or

neuroplasticity [91], in accordance with the often short-term alleviation of symptoms that occurs in patients. Few if any studies have investigated neuroadaptation that occurs after truly long-term use. In patients, it is uncertain whether the changes induced by antidepressants revert to their original state upon discontinuation or if they persist. While a number of animal studies of the effects of benzodiazepine exposure have shown neuroadaptation and changes, many have been focused on tolerance, dependence, and withdrawal [92–96] and so it is unclear to what extent these findings are relevant to these types of persistent syndromes in clinical populations.

While research on long-term effects of drugs used to treat mood and anxiety in clinical studies is ongoing, it has already been shown that other psychotropic medications, such as antipsychotics, can lead to lasting brain alterations, including tardive dyskinesia [97]. Other potential long-term impacts of mood and anxiety medications also include "legacy effects", withdrawal, and rebound effects [98, 99]. "Legacy" effects are defined as the persistent impact that a medication has on an individual even after drug use has been discontinued. For example, persistent cognitive effects have been shown in individuals even after stopping or abstaining from benzodiazepine use, including impairments in recent memory, processing speed, visuoconstruction, divided attention, working memory, and sustained attention [70].

Withdrawal effects, which refer to the symptoms that occur when a person reduces or stops taking a drug, indicate that there are physiological changes that take place in response to the presence of a drug. These may include predictable "rebound" reactions, like anxiety after benzodiazepine withdrawal [100], poor sleep after medication used for insomnia [101], and hypersensitivity to pain in opiate withdrawal [102]. Similarly, antidepressant withdrawal can range from mild to severe, with many experiencing significant symptoms lasting weeks to months, and sometimes longer [103].

Benzodiazepine withdrawal can be protracted, persisting for months or even years, with symptoms like anxiety, tinnitus, and tingling [104]. More recently, studies focusing on consumer use have shown protracted withdrawal from antidepressant use ranging between 5 to 166 months including most common symptoms of emerging mood instability, suicidality, dizziness, brain zaps, headache, and fatigue [105]. Further complicating things, these types of late onset or persistent symptoms may be misinterpreted as warning signs of a relapse of the disorder [103].

These examples indicate the need for better long-term clinical and translational studies to more accurately represent the complexities of real-world utilisation of mood and anxiety medications. This includes examining potential neurobiological alterations over extended periods and assessing post-discontinuation effects to provide more information of benefits and risks, thereby contributing to more effective and evidence-based prescribing practices.

CONCLUSION

This brief survey and comparison of results from animal and clinical studies highlights the crucial interplay between animal models and clinical investigation. On the one hand, animal models can be faulted for not fully recapitulating all of the relevant features of the human condition. On the other hand, clinical understandings of these conditions are often shaped by a medicalised framework of mental health, which may lead to treatment approaches grounded in mechanistic assumptions that have failed to be borne out in animal models or translational studies. In other words, the problem is bidirectional. What we are often left with is treatment that insufficiently addresses the complexity and heterogeneity of the actual clinical presentation, response to treatment [106], or the full treatment context, and instead looks for biologically-defined druggable targets that, at best, can be said to be correlated with disease presentation, and at worst, may be exacerbated by drug treatment. Translational research thus ends up stuck in a loop of perpetual failure. The persistent challenge in developing consistently effective treatment approaches is a testament to the seriousness of this issue. Continuing along the same trajectory without addressing foundational assumptions is unlikely to yield meaningful progress.

Admittedly, this is a somewhat dire assessment and prognosis. We hope, however, that the seeds of an effective translational approach are found here. Our conceptual and diagnostic framework must shift to encompass the entire disease trajectory and context, including the therapeutic context and ongoing effects of drug treatment on symptoms and functioning, rather than doubling down on the search for poorly-defined and elusive biomarkers or druggable targets. While a thorough enumeration of approaches to translational research is beyond the scope of this article—and in some ways beyond the scope of current thinking and conceptualization—we offer some practical suggestions in conclusion.

First, behavioral tests should be vetted to ensure that they are valid proxies for the mental and emotional processes of interest in human mood disorders. Crucially, improving the validity of behavioural tests requires a more precise definition of what constitutes a mood disorder in clinical settings. Rather than relying solely on symptom-based constructs, we should aim to model key dimensions of suffering and functioning, such as anhedonia, emotional regulation, interpersonal connectedness, or role functioning, that better reflect the lived experience of mood disorders.

Given the substantial heterogeneity in mood disorders as discussed above, it is increasingly clear that conceptualizing mood disorders as singular diseases with uniform underlying biology and symptoms is an oversimplification. Instead, we suggest adopting a drug model perspective [107], wherein different psychiatric medications are viewed as tools to target specific symptom profiles rather than to correct an underlying pathophysiology. This reframing suggests that different individuals experience distinct symptom clusters and may respond variably to specific pharmacological effects. Accordingly, animal models should move toward specificity, targeting discrete symptom dimensions or behavioural phenotypes relevant to particular clinical presentations, and evaluating how candidate treatments influence these defined outcomes (the NIMH RDoC initiative is moving in this direction [108]). Such an approach could enhance translational validity by aligning preclinical testing more closely with the nuanced, multidimensional nature of mood and anxiety disorders.

Our ability to infer efficacy of treatment strategies stands and falls with the validity of our behavioural measures. This is likely one of the most challenging aspects of modelling mood and other psychiatric disorders in animals. While most studies have focused on the high-throughput tests discussed above, a number of investigators are working to develop and test translational experimental protocols for rodents that are functionally analogous to those used in humans [109, 110]. This work is crucially grounded in rigorous behavioural analysis of motivational and cognitive processes, and is thus able to parse apart aspects of disease symptomology with direct relevance to human patients [111]. Results from these studies are beginning to provide more detailed insight into the behavioural and motivational effects of antidepressants [112]. These next-generation methods in combination with optimization of already-existing protocols that model a developmental trajectory for disease, as in chronic stress models of depression [113, 114] offer great promise for the future of translational models [111]. For example, animal paradigms employing chronic stress have demonstrated that prolonged exposure to stress can induce mood-related behavioural impairments. Importantly, these findings highlight that such mood

disturbances may represent normal adaptive responses to adverse environments rather than evidence of an intrinsic neurophysiological defect (and multiple "hit" models show the interplay between genetic susceptibilities and environmental insults). Rather than seeking solely a pharmacological or neurophysiological "fix," these models invite us to interpret mood disorders as signals reflecting the impact of social and environmental adversity. Unlike animals confined to their environments, humans possess the capacity to alter their circumstances, underscoring the critical role of environmental and social interventions. Consequently, these insights reinforce the importance of applying the biopsychosocial model not only to the assessment of mental illness but also to its treatment, recognizing that effective intervention requires addressing biological, psychological, and social factors in concert.

Second, we need to ensure that our models of treatment recapitulate, to the extent possible, the relevant features in human treatment regimens. An obvious start here is to assess the long-term effects of various drug treatments on a similar timescale as occurs in clinical practice. Furthermore, a particular challenge with modelling disorders that have a uniquely subjective component is that it may not ever be possible to accurately capture all of the relevant facets in an animal model. Being brutally honest with ourselves about this reality will require us to be more humble about the scope and reach of our existing animal models and will force us to engage more meaningfully with the clinical literature on which our models are purportedly based.

In summary, on a foundational level we need to recognize the fundamental disconnect between the clinical therapeutic experience and the simplified medical model of disease that is so prevalent in psychiatry and animal models. Acknowledging this and being aware of the limits of our methods and being innovative in our approaches to modelling these conditions in animals is critical. This will be challenging for sure, but represents a way forward towards a truly effective translational treatment approach for mood disorders.

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AUTHOR CONTRIBUTIONS

VT and RW both conceptualized the article, conducted literature reviews, wrote, revised, and edited the manuscript. Order of authorship is alphabetical.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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