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Treatment-resistant depression reconsidered

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ABSTRACT

The term treatment-resistant depression (TRD) has been the focus of hundreds of studies and clinical trials, though it is not a diagnosable mental health condition according to current clinical standards. The term implies depression that is particularly difficult to treat. However, as we illustrate here, the use of the TRD construct creates significant concerns regarding patient welfare and optimal distribution of resources. First, TRD is frequently defined as depression that failed to respond to antidepressant medication. Therefore, patients may be labeled with TRD after having tried just one medication, without consideration of effective non-pharmacological treatments such as psychotherapy or holistic interventions to improve sleep, nutrition, and exercise. Second, TRD implicitly contextualizes depression as a problem within an individual's brain, ignoring larger systemic, developmental, and sociological factors known to be depressogenic. Important structural determinants of health such as social isolation, environmental stressors, systemic oppression, unmet basic needs for shelter, food, and safety are excluded. Third, TRD does a disservice to patients when it rapidly escalates treatment decisions to increasingly risky and experimental options. And finally, the existing concept of TRD is used to justify enormous financial investment – on the order of billions of dollars - in research aimed at identifying precise biological treatment targets. The quest for biomedical treatments struggles to provide the anticipated return on investment in the form of decreased depression burden despite over 50 years of costly effort. Drawing from historical perspectives, we highlight these issues and propose recommendations to address them.

Patrick is a 16-year-old high school sophomore overwhelmed by the demands of his college preparatory schoolwork and extra-curricular activities, including violin lessons and volunteering to read to elderly residents of a local nursing home. His parents moved multiple times when he was growing up, which interfered with his ability to make and retain friendships. He was just starting to feel comfortable in his high school when his girlfriend broke up with him and his friend group fell apart. He stopped participating in school and enjoyable activities, reported difficulty concentrating, and, according to his father, "moped around all day." His parents took him to his pediatrician who prescribed an antidepressant for major depressive disorder. Three months went by without improvement. His doctor referred him to a psychiatrist, who prescribed a different antidepressant. Months went by with numerous changes in medication and various side effects, but still no remission. The psychiatrist suggested that Patrick consider psychotherapy, specifically cognitive behavioral therapy (CBT), but he declined because he did not think it would be helpful. Patrick began to express hopelessness about ever feeling better. The psychiatrist diagnosed him with treatment-resistant depression and recommended electroconvulsive therapy (ECT), which he referred to as a life-saving treatment. Patrick received 14 ECT treatments. His parents thought that his depression lifted a modest amount, but Patrick reported feeling more hopeless about his future. He sometimes forgot the names of his friends, and he felt alienated and socially awkward as he struggled with memory issues and low mood. He became increasingly despondent about the failure of treatment, and his life was dominated by depression and clinical visits. The doctor recommended that he enroll in an experimental trial for ketamine infusion.

This case, based on an amalgam of several cases we have encountered in our clinical practice in the United States, exemplifies several growing problems in psychiatry. Patients are labeled with treatment-resistant depression (TRD) after not responding to one or two antidepressants and then are promptly offered increasingly risky interventions (that is, interventions that have adverse reactions) that do not consider or target the underlying source of distress in the context of the human experience. In this paper, we detail historical trends and definitions of TRD, illustrate harm caused by the definition, highlight major gaps in care and

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prevention, and offer recommendations for refinement of the definition of TRD.

1. How we got here: Definitions of treatment-resistant depression

The term treatment-resistant depression (TRD) has received considerable attention from researchers (with a Google Scholar search of this term conducted in July 2021 resulting in 50,500 results). Although a sizeable proportion of top-cited articles on TRD are written about how best to define it, it is not in any of the editions of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), and there is no universally accepted definition of TRD. The majority of studies define TRD as failure to respond to one or two antidepressant medications (Brown et al., 2019; Fava, 2003).

Formal attempts to classify individuals with depression into "responders" and "non-responders" date back to at least the 1970s (Levine & Raskin, 1974), when psychiatrists became interested in classifying those patients who responded to medication and those who did not (see Scott, 1991 for discussion of "chronic depressives" and "treatment resistant" subtypes of depression); various rubrics to stratify disease severity have since been used. In 1997, two psychiatrists (Thase & Rush, 1997) used the oncological disease staging models to inform a new model of treatment resistance that delineated five stages according to the cumulative number of psychiatric intervention failures:

Stage I	Failure of at least one adequate trial of one major class of antidepressant
Stage II	Stage I resistance plus failure of an adequate trial of an antidepressant in a distinctly different class from that used in Stage I
Stage III	Stage II resistance plus failure of an adequate trial of a tricyclic (TCA)
Stage IV	Stage III resistance plus failure of an adequate trial of an MAOI
Stage V	Stage IV resistance plus failure of a course of bilateral ECT

This model may be appealing in principle, but several caveats diminish its utility. For instance, "adequate trial" and "failure" are not defined (Fava, 2003) and resistance is formulated in response to biomedical interventions only (medication and ECT). There is no mention of psychotherapy or other holistic interventions in this definition of treatment resistance. The causal relationship between antidepressant medications and symptom relief have been questioned based on methodological issues that diminish awareness of the placebo effect (Kirsch, 2014; Moncrieff, 2008). Furthermore, some scholars note that the staging model is predicated on outdated efficacy data for antidepressants; meta-analytic data comparing antidepressants head-to-head show largely equivalent effect sizes regardless of comparing medications within- and between-classes (which demonstrates no substantial difference between within-class antidepressant switches and between-class switches [e.g., Cipriani et al., 2018]).

It may be useful to create terms that categorize individuals who continue to suffer from depression after treatment. Ideally, the goal of such a term would be to raise awareness and increase access to holistic interventions (i.e., those that take into consideration social, physical, psychological, and experiential factors) that work, distinct from the subset of treatments that have not been effective. Empirically, however, TRD is rarely used to promote holistic care. Because no single entity owns the concept of TRD, there may exist multiple rationales for the use of this term. There are conceivable motivations for professional and industry forces as well as individual researchers and clinicians.

There are several historical reasons for the exclusive focus on biomedical treatments in most definitions of TRD. In the 1970s, the construct of depression evolved in relationship to the symptoms that abated with medication treatment. The diagnosis of depression did not represent an entity in nature awaiting a therapy, but rather, it was an entity defined by its responses to an existing therapy (Healy, 1997; Hirshbein, 2009; Lane, 2007; Smith, 2012). Further, the scales to measure improvement were developed in direct response to outcomes observed after medication treatment. The Hamilton Depression Scale (Hamilton, 1960), for example, intentionally included symptoms that captured observable changes in patients who received trials of tricyclic antidepressants (TCAs). As Moncrieff (2008) describes in her historical analysis of the invention of the concept of antidepressants, the psychiatric profession shifted from a "drug-centered" model that described how psychoactive medications affected a person's experience to a "disease-centered" one that describes how medications target purported underlying diseases (see also Moncrieff & Cohen, 2005). Thus, as many critics have pointed out, the construct of depression as a medical disease is linked to drug development as well as to the sociopolitical and economic forces that supported that development. The ecological validity of the construct itself is questioned by scholars who address this issue more thoroughly than we can in this limited discussion of TRD (see Conneely, 2021; Greenberg, 2010; Moncrieff, 2008; Pilgrim & Bentall, 1999).

In industry settings, profit motives lead pharmaceutical companies to generate expanded markets for medications (Frances, 2013). This profit motive is a major driving force for drug development that has led to life-saving medications for previously untreatable diseases. When unchecked, however, the profit motive, combined with misleading marketing rhetoric, can have catastrophic consequences. The US opioid epidemic is a real-world worst-case scenario, in which an addictive end-of-life acute pain medication, morphine sulfate (MS Contin) and its more potent successor, oxycodone (OxyContin), were promoted as a safe treatment for all forms of pain (Herzberg, 2020; Keefe, 2021). The risk of addiction was minimized and professionals who warned about the risk were demonized and ridiculed as having "opioidophobia" (Keefe, 2021). Likewise, TRD's exclusive focus on medication reinforces pharmaceutical marketing campaigns that promote the sale of antidepressant medications and minimization of risks. Antidepressant medication risks include serious and even life-threatening side effects (e.g., changes in cardiac rhythms, increased suicidal ideation, seizures, hyponatremia, erectile dysfunction, venous thromboembolism, bleeding, itchiness, stomach upset, and weight gain [Carvalho et al., 2016]). Beyond side effects, recent publications describe the previously overlooked risks of withdrawal effects and persistent sexual side effects after withdrawal (Healy, 2019; Bala, 2018; Moncrieff, 2020).

An example of an expanded market is seen with brexipiprazole (Rexulti), an atypical antipsychotic. It secured FDA approval in 2015 both as a treatment for schizophrenia and as an adjunct medication for individuals with depression who only "partially responded to an antidepressant" (another phrase for treatment resistance). One TV advertisement for Rexulti begins with, "Even when you're taking an antidepressant, you may still be struggling with depression". Lundbeck, the pharmaceutical company that developed Rexulti, also manufactures several antidepressant medications including top-selling Lexapro, Celexa and Trintellix. Thus, the same company profits from the original medication marketed to treat depression and gains additional profits from the medication marketed to treat the expected high rates of failure to respond to the original medication (the treatment resistance). This would not be a great concern except that there are serious risks associated with these medications (Carvalho et al., 2016; Newcomer, 2004), and their effectiveness is less than one is led to believe by direct-to-consumer marketing. In short, pharmaceutical companies are heavily incentivized to maintain the current terminology of medication-based treatment-resistance.

Institutions and individual researchers also play a role in perpetuating the focus on medications and TRD. Researchers seeking to sustain academic research labs in a tight funding climate may seek financial support from pharmaceutical companies that implicitly promote the biases in the TRD framework. Shifts in patterns of third-party payment have reinforced the medicalization of psychological distress, with an emphasis on physician diagnosis and prescriptions more than broad-based

interventions such as individual or family psychotherapy, health behavior changes or lifestyle coaching (Frank & Glied, 2006).

There are numerous reasons for the widespread use of the term TRD, and it is unlikely that any one entity is promoting the term for nefarious reasons. However, in practice, the use of the term causes harm. We highlight some of the salient problems below, building on an earlier critique of the term compiled by the Agency for Healthcare Research and Quality in partnership with the US Department of Health and Human Services (Gaynes et al., 2018).

Problem 1. Definitions of TRD ignore nonpharmacological treatment.

By restricting the definition of treatment to medications, TRD implicitly perpetuates the notion that psychiatric medications should be the first-line (or only) treatment for all types of depression. A thorough analysis of the data reveals that antidepressant medications are only marginally better than placebo (Kirsch, 2010, 2019), with meta-analyses revealing small and not clinically significant benefit over and above placebo conditions (Cipriani et al., 2018; Kirsch et al., 2008; Moncrieff, 2018). The large placebo response in antidepressant trials is so prominent that a recent study attempted to minimize it by teaching patients to disregard their placebo-induced improvements in order to test a coaching protocol designed to make psychotropic medications appear more effective (Cohen et al., 2021). This is not to say that antidepressants are unhelpful; it is to acknowledge that they only marginally outperform pharmacologically inert compounds, which suggests the importance of non-pharmacologic elements of treatment.

Most importantly, the narrow focus on medication negates the vast body of clinical research demonstrating that a wide range of psychosocial interventions are effective for depression. Psychological therapy, including behavioral activation (Sturmey, 2009), cognitive therapy (Hollon et al., 2005), and psychodynamic psychotherapy (Leichsenring & Schauenburg, 2014), are a few exemplars that have demonstrated effectiveness in reducing depressive symptoms as much as medications, and typically show effects enduring longer than medications once treatment has stopped (Cuijpers et al., 2013; Hollon et al., 2021). A recent set of network meta-analyses also revealed that psychotherapy alone or in conjunction with medication outperforms medication alone (Furukawa et al., 2021). Psychotherapeutic options build resilience, teach patients skills to utilize their emotions, recognize the source of their distress, and create more fulfilling lives, beyond the duration of treatment. In fact, there are hundreds of forms of effective psychotherapy with core commonalities (Wampold, 2015). Other modifiable behavioral determinants of health such as exercise, adequate sleep, maintaining a healthy body weight, nutrition, and avoiding problematic use of substances such as alcohol, tobacco, and cannabis are all linked with decreased incidence of depressive symptoms (Cairns et al., 2014; Carek et al., 2011; Sarris et al., 2015; Sathyanarayana Rao et al., 2008). Yet, they are also not considered in any definitions of TRD.

Failing to consider psychosocial interventions in the TRD definition removes them from discussions between healthcare providers and patients. This is unfortunate and ironic, as psychotropic medications were originally promoted to facilitate the patient's growth in psychotherapy (Hoch, 1959). Ultimately, the failure to include psychosocial treatments in these discussions diminishes patient awareness of their existence and therefore decreases patient access to them. In addition, as our case example illustrated, when patients are offered a referral for psychotherapy, many lack confidence that a non-medical intervention will help, which is not surprising, given pharmaceutical marketing campaigns and the effective marginalization of non-pharmacological interventions.

Neglecting psychosocial avenues in the TRD framework also does a disservice to mental health clinicians and trainees. Psychiatry residency programs that embrace the TRD framework implicitly teach residents that psychiatric medications are the primary tool to treat depression. The TRD framework shuttles these new clinicians away from developing expertise in the humanistic aspects of caring for individuals with depression. That is, mental health clinicians are disempowered and limited by the TRD framework. Consequently, patients are offered a limited range of treatment options and many experience iatrogenically compounded hopelessness when one, two, or three antidepressants have failed, and their distress becomes increasingly medicalized as a severe or malignant depression. It is not uncommon to hear clinicians and patients express fear that an individual will not recuperate from depression based on having tried multiple antidepressants. Acceptance of unsolvable problems is a healthy behavior (Fuchs et al., 2013), but TRD shunts the process of personal discovery and promotes the belief that potentially solvable problems are unsolvable.

Problem 2. The TRD framework focuses on brain pathology and ignores life context.

A second problem with the current TRD framework is that it gives undue influence to brain pathology as an explanation for depression (Akil et al., 2018). Several large-scale pharmaceutical and anti-stigma campaigns have marketed and disseminated the notion that depression is caused by a chemical imbalance in the brain, a simplistic reduction that is scientifically unproven (Deacon, 2013; Harrington, 2019; Whitaker, 2010). While proponents of this messaging argue that it can help decrease blame and promote help-seeking, there are several downsides to holding these biomedical-centric beliefs, including hampered treatment response and increased stigma (Kvaale et al., 2013). In both thought experiments (Deacon & Baird, 2009; Kemp et al., 2014; Lebowitz & Ahn, 2015) and in clinical settings (Lebowitz et al., 2021; Schroder et al., 2020), believing that depression is predominantly due to genetic or chemical imbalance factors is related to poorer expectations for improvement and treatment outcomes. Moreover, in one study, providers who espoused more biogenetic viewpoints were perceived as less empathic (Lebowitz & Ahn, 2014), which is troubling considering that the therapeutic relationship is one of the most robust predictors of treatment response (Flückiger et al., 2020) and is predicated on empathy. Thus, TRD's implicit focus on brain pathology may inadvertently hamper treatment progress.

Life context plays a major role in the development of depression. The most helpful framework for conceptualizing depression is that of a multifaceted, phenomenological experience influenced by variables in multiple domains. Social circumstances, physical environment, financial issues, conscious and unconscious psychological factors, and physiological factors such as sleep, hormones, inflammation, illness, and physical fitness all contribute to a person's emotional well-being. It is well-established that the experience of depression is modifiable through multi-modal, holistic interventions (Conneely et al., 2021; Sarris et al., 2015), yet these aspects of treatment are easily overshadowed and neglected when the mechanism of depression is presumed to be solely a brain disease (Siegel, 2007). To be fair, there are biomedical phenotypes of depression due to physical illnesses that physiologically cause emotional distress, fatigue, and malaise (thyroid hormone problems or pro-inflammatory induced sickness behavior triggered by physical injury, a cold or flu, for example, Hage & Azar, 2012; Kelley & Kent, 2020), yet, ironically, phenotypes of depression caused by these biological factors are specifically excluded from psychiatric nosology. Philosophical perspectives have suggested that depression can be an understandable and meaningful distress response to environmental stressors and adversity (see Conneely et al., 2021; Lafrance & Stoppard, 2006). From these perspectives, the emotional experience becomes a call to action, and the resistance to biomedical treatments arises because the root cause has not been addressed. Patrick's case demonstrates a confluence of social, environmental, and developmental factors known to contribute to depressive symptoms, yet no attempt was made to target these elements specifically.

Problem 3. TRD promotes unnecessary escalation to higher risk and experimental interventions.

The use of TRD encourages clinicians to offer and patients to seek higher intensity treatments that carry significant risks. The exclusion of non-pharmacological treatment modalities facilitates the use of TRD as a

justification to enroll patients in more invasive, expensive, risk-laden and/or experimental treatments, such as electroconvulsive therapy (ECT), ketamine, vagal nerve stimulation (VNS), deep brain stimulation (DBS), magnetic seizure therapy, and transcranial magnetic stimulation (TMS), without a trial of psychosocial interventions first (Daly et al., 2018; Singh et al., 2016). In our case example, Patrick received multiple antidepressants, ECT, and a recommendation to explore ketamine, all without ever receiving any lower risk nonpharmacological interventions.

Taking one example of this escalation, let us look at electroconvulsive therapy (ECT). ECT involves giving patients general anesthesia before inducing a seizure with a small current of electricity. It can be a critical intervention for some seriously ill patients, but it comes with significant cognitive side effects, including memory loss and difficulties with processing new information and creating new memories (Loo, 2008). ECT is one of the oldest treatments still in use within psychiatry (Shorter & Healy, 2007). At the time of its introduction in the US in the late 1930s, it was seen as an important tool to manage unruly patient populations in overcrowded hospitals (Braslow, 1997). In its early years of use, memory side effects were not considered a risk that outweighed the benefits. By the 1970s and 1980s, though ECT had been modified by anesthesia (which confers another set of risks), it was seen as old fashioned by psychiatrists and as a problematic symptom of an abuse of power by psychiatric critics. In recent years, ECT has had a comeback as an intervention to use when medications seem to fail (Hirshbein, 2012).

ECT has played a role in the evolution of the definition of TRD. As early as 1981, treatment resistance was defined in terms of the need for ECT for patients (Paul et al., 1981). The concept of TRD is used to justify a skewed risk/benefit analysis that minimizes side effects of medications and higher risk modalities based on the circular reasoning that the condition of TRD is so serious that it requires more risky, invasive measures. (Of note, this was the same mentality that fostered enthusiasm about frontal lobotomy in the 1950s [Pressman, 1988]). In ECT, for example, modern proponents have minimized the cognitive side effects and assured patients that they need not be concerned, even as some patients report profound memory loss and cognitive deficits that could be considered a form of brain damage (Andre, 2009). While some patients are so profoundly impaired that the risk/benefit ratio of ECT makes sense, the TRD definition determines patients' severity based on medications the patient has tried before rather than the state of the patient or an exploration of alternative, less invasive options (see also Mattes, 2021 and Rues, 2021 for reservations regarding recommendations for the widespread use of ketamine for individuals having tried two medications).

Problem 4. Current TRD definitions direct resources away from effective treatments and preventive public-health based population interventions.

Despite the implicit need for better treatments embodied in the term treatment resistant depression, many current studies of TRD are iterations of decades-old biomedical intervention trials that have not led to clinical breakthroughs. A September 2021 search for "treatment-resistant depression" on www.grantome.com, a publicly available database for most governmental funding agencies, is illustrative. The search was limited to R01 grants from the National Institutes of Health (NIH) in the year 2019. Of the 21 results that yielded abstracts mentioning treatment-resistant depression, eight used biomedical interventions (1 antidepressant medication study, 3 ketamine studies, 2 seizure therapies [magnetic seizure therapy and ECT], and 2 transcranial magnetic stimulation studies), and seven focused on animals (mice and non-human primates). None of the studies evaluated psychotherapy or behavioral interventions for TRD. Torrey et al. (2021) noted the National Institute of Mental Health (NIMH) has increasingly funded studies to uncover biomarkers at the expense of fewer treatment trials. Hundreds of millions of taxpayer dollars are spent each year funding investigations that examine brain responses among individuals who are healthy and compare them to individuals with a diagnosis. Yet this approach has not resulted in the boon of treatment options for patients (Deacon, 2013) that one would hope for with such expenditures. Tom Insel, the former director of NIMH, admirably critiques his own leadership and indirectly warns about the pitfalls of hyper-focusing on biomedical research in mental health. In a 2017 interview, reflecting on the research that was funded during his tenure, he said he "[does] not think we moved the needle in reducing suicide, reducing hospitalizations, [or] improving recovery for the tens of millions of people who have mental illness" (Rogers, 2017).

TRD has been used as an exemplar of a type of depression for which biomarkers and the organic cause have not yet been discovered and therefore appropriate treatment has not yet been developed. With its focus on medications to target an implied but unknown brain pathology, the current TRD paradigm inflates the clinical relevance of psychotropic drug development. Unfortunately, TRD, as currently conceived, is not likely to yield an ecologically valid study population, given the heterogeneity of patients who have failed to recuperate after trying medications only. Patients who did not respond to medication but were not given psychotherapy cannot be considered inherently different than patients who recuperated through psychotherapy. Establishing biomarkers and brain mechanisms of depression may be a worthy pursuit; however, using the TRD framework as a category of patient to motivate this research is less helpful. The TRD framework drives the scientific community to invest valuable time, money, and attention into developing new treatments while there are many nonpharmacological approaches already available for those with what is called TRD.

2. Recommendation 1: Include nonpharmacological treatments in definitions of TRD

In order to promote effective treatment and identify individuals who have depression that is legitimately resistant to *[all appropriate]* first line treatments, we must include psychotherapy, behavioral, and lifestyle interventions in the criteria for definition of TRD. An accurate representation of treatment resistance would require that, to be classified as treatment resistant, a patient would have failed non-pharmacological interventions in addition to antidepressant medication. Interviews to establish TRD would need to inquire not only about medication trials, but also about past behavioral interventions, lifestyle choices, and trials of psychotherapy. Nutrition and exercise are not typically discussed as part of mainstream psychiatric interventions but including them in definitions of TRD would encourage professionals to consider how to help patients optimize these variables. We recognize that not all psychotherapeutic interventions are of equal quality, and this creates a challenge for incorporating psychotherapy into the definition of TRD. Some therapists offer a generic space for patients to vent, whereas others tailor interventions to the patient's specific needs. It is beyond the scope of this paper to delineate what constitutes an adequate course of therapy, but the quality and quantity of psychotherapy need to be accounted for in criteria for TRD (Conway et al., 2017; Markowitz et al., 2022; Peeters et al., 2016).

3. Recommendation 2: Consider holistic systems-level social, environmental, psychological, and physiological etiologies of depression

Clinicians, researchers, educators, policy makers, and the general public are all affected by the TRD framework. With this recommendation, we invite all to consider broadening the conversation beyond professional and industry silos toward more holistic shared ownership of depression and its treatments. The World Health Organization estimates that between 30% and 55% of health outcomes are attributable to social determinants of health (https://www.who.int/health-topics/social-determinants-of-health#tab=tab_1). In alignment with this recommendation, recent work (Metzl & Hansen, 2014) has suggested that medical education consider larger systemic, institutional, and political structures that contribute to poor health. It is well documented that mental health problems are exacerbated

among those with low socioeconomic resources (Cutrona et al., 2005; Miech & Shanahan, 2000). Major life stressors, which are perhaps the most robust identifiable cause of depression (Kendler et al., 2010) are much more common among individuals in lower income groups (Lever, 2008). A recent systematic analysis revealed a robust association between income inequality and greater mental health concerns (Tibber et al., 2022). Education level is another universally relevant social factor inversely associated with depression (Bjelland et al., 2008). Considering these contextual sources of depression would improve the utility of our collective thinking about TRD.

4. Recommendation 3: Stop using the current definition of TRD as criterion for offering higher-risk interventions

Given that the TRD framework relies on critically questioned data supporting the use of antidepressants and that it ignores effective, lower risk holistic approaches, using TRD as the criterion for entry into more risky, invasive, and/or experimental treatments cannot be considered evidence based. Low risk non-pharmacological interventions should be tried prior to interventions such as ECT, ketamine, VNS, DBS, magnetic seizure therapy, and TMS. Once the definition of TRD has been modified to include behavioral and lifestyle interventions, it could be logical to use that new definition of TRD in algorithms to empower patients and clinicians to decide how to proceed. While we advocate for modifying the existing concept of TRD to improve care within the existing framework of depression, it should be noted that the debate about the legitimacy of depression as a disease could lead to broader sweeping suggestions for change. That level of critique is beyond the scope of this paper (Aftab, 2022), but we refer interested readers to additional work of scholars who propose that less medicalized models of understanding the human emotional experience are more empowering and respectful of human agency (Greenberg, 2010; Moncrieff, 2020).

5. Recommendation 4: Advocate for funding of non-pharmacological studies and programs to support well-being

Given the overwhelming evidence that behavioral and social determinants of mental health are powerful and modifiable (Compton & Shim, 2015), we urge public office-holders, public and private funders, educators, fellow mental health professionals and researchers to advocate for broad-based non-pharmacological interventions to enhance well-being and diminish the development and persistence of depression. We recommend that funding agencies prioritize and dedicate resources to implementation studies utilizing existing information for practical prevention and treatment of depression. Moving beyond the focus on pharmacological and brain-based technological studies could contribute greatly to public well-being. Increasing the number of high quality diverse social-systems based research, treatment and prevention programs would likely lead to direct positive effects on public health.

6. Concluding remarks

The construct of TRD – based almost exclusively on failed medicine trials - is a product of the social, intellectual, political, and economic forces over the last fifty years. Although it was designed with good intentions in mind, it has not led to the expected improvements in psychiatric care from the patient perspective. As we illustrated here, it has had the opposite effect of limiting access to viable non-pharmacological treatments and has unnecessarily promoted higher-risk interventions.

There is not a one-size-fits-all cause or solution to remedy the social problem of depression. As we know from the seminal work of experts who have explored individual differences in reactions to adversity, one individual may thrive in a given circumstance, while another may languish (Csikszentmihalyi, 1990; Frankl, 1962). As a society, we make choices about what to prioritize as collective values and goals. Structural determinants of health, such as systemic biases, inequities, cultural norms, policies, and institutionalized oppression are, in fact, also products of our time and location (Crear-Perry et al., 2021). There are many pathways to recuperate from depression, and our hope is that updates to the concept of TRD will facilitate broader access to a greater variety of pathways.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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