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Pragmatic treatment options for depression and anxiety disorders are needed

Major depressive disorder (MDD) is a common disorder with a lifetime risk around 35%¹. It is a significant cause of mortality and the second leading cause of years lived with disability worldwide². At many levels, the similarities between MDD and the anxiety disorders are much stronger than the differences. For instance, these disorders share genetic, temperamental and environmental risk factors, frequently co-occur, and cognitive behavior therapy (CBT) and antidepressant drugs are recommended as principal treatments for both³. It will therefore be very difficult to locate pathologies and treatments that are specific to subtypes of depression without considering their relationship with anxiety. As a result, we broaden our comment on Perlis' proposal⁴ to reduce personalized (or non-evidence based) medicine in favor of precise (evidence-based) medicine to include both depression and anxiety.

Despite the availability of evidence-based treatments and the energetic "Reduce Mental Illness" campaigns that have been carried out in many countries, the years lived with disability due to these disorders have not declined over the past two decades². This burden persists, at least in part, because only 39% of adults who met criteria for a depressive and/or anxiety disorder in the past year sought help for their mental health problems⁵. Additionally, the burden associated with depression and anxiety continues, as Perlis suggests, because of the type and dose of treatment that patients receive from their mental health professionals.

Evidence-based guidelines for the treatment of depression and anxiety recom-

mend a stepped approach to care where patients are prescribed treatments in order of their intensity, effect and cost⁶. Specifically, CBT is the recommended first-line psychological treatment for mild to moderate depression and the anxiety disorders, and in combination with pharmacotherapies for severe and complex cases^{7,8}. Although these guidelines were developed to translate advances in medical research into clinical practice, their dissemination does not necessarily improve clinical outcomes. Indeed, of those people who met criteria for depression and/or an anxiety disorder in the past year and sought help for their mental health problems, 67% were offered an evidence-based treatment and only 41% received a minimally adequate dose of treatment⁵.

Even when people receive a minimally adequate dose of treatment, a significant proportion continue to experience distress and impairment. This is because the recommended psychological and pharmacological interventions range in number needed to treat (NNT) from ~2 to 16, depending on the comparator⁹. Perlis argues that the NNT of antidepressants could be improved if: a) specific drugs were linked to specific disorder subtypes; b) diagnostic tools sensitive to these mechanisms of action were disseminated; and c) clinicians implemented these tools in practice. To this end, he states that "numerous investigations of predictors... of treatment response have been reported over the past five decades"⁴. Yet, to our knowledge, none of these predictors have been associated with Level 1 evidence that a certain treatment for MDD is superior for people who have certain characteristics. Level 1 evi-

dence would require both independently replicated superiority (RCTs) with representative groups of patients in which the treatment is shown to remedy the core pathology in the target group *and* that there are no methodologically sound rebuttals.

We thank Perlis for mentioning a five-decade time frame. Five decades ago, we, in a study to identify core pathologies, divided a cohort of inpatients with a primary diagnosis of depression into those with "endogenous" or "neurotic" depression on the basis of clinical presentation, family history and longitudinal data. At intake, discrimination between endogenous and neurotic depression was strong, but the data were equally compatible with Grinker et al's five-division classification¹⁰, which weakened the findings. At the 15-year follow-up, the overall outcomes of people identified with endogenous or neurotic depression were equally poor, with two relatively minor differences: endogenous depression showed more frequent but shorter hospital admissions, and the outcome in neurotic depression was more strongly related to the level of neuroticism at the index admission¹¹.

Identifying disorder subtypes for targeted treatment, as Perlis says, is likely to be time consuming and difficult. Indeed, seven types of first line drug therapies for MDD – selective serotonin reuptake inhibitors (SSRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), norepinephrine-dopamine reuptake inhibitors (NDRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), noradrenaline reuptake inhibitors (NARIs), melatonin agonists, serotonin modulators – that notionally target different pathologies are

listed in a recent clinical practice guideline⁷. If the relative power of each is weak, then superiority trials will need to be very large, costly and time consuming once it has been decided that the patients with the core pathologies can be reliably identified. The feasibility of such trials is questionable.

The possibility of identifying mechanisms of change that are associated with subtypes of depression and anxiety is attractive. In reality, it is likely that this will not occur for many years. We are mindful that the burden of these disorders is large and immediate. We therefore turn to practical ways of averting this burden that are available now. Studies that show that primary care patients prefer psychotherapy over antidepressant treatment¹², that psychotherapy alone has comparable long-term outcomes to combined treatment¹³, and that the number needed to harm (NNH) associated with antidepressants can be considerable¹⁴, support the extant recommendations for psychological interventions as first-line treatments.

Yet CBT suffers from four deficits in comparison to antidepressant medication. It is more difficult to prescribe, it is more expensive, quality in practice cannot be guaranteed, and it is not widely available outside major city centers. Auto-

mated Internet-delivered CBT (iCBT) is equally effective as face-to-face CBT¹⁵, yet inherently more scalable and therefore offers a more efficient use of scarce public health resources. It is as easy to prescribe iCBT as it is to prescribe medication, and the fidelity of treatment is guaranteed across service providers.

One big advantage of iCBT compared to face-face CBT and antidepressant medication is that RCTs are relatively simple and quick to do. If patients can be screened over the Internet and do not have to be seen in person, then a large trial can be finished within six months of institutional review board approval. A rapid cycling research model would allow us to search for specific-treatments-for-specific-group pairings by running several trials at the same time. We would no longer have to wait 15 years for a null result.

In conclusion, Perlis emphasizes “the need for changes in how depression care is delivered, measured, and used to inform future practice”. We agree: the uptake and quality of mental health care that is delivered in the community needs immediate improvement. While disorder-specific targeted treatments are yet to be developed, iCBT is an evidence-based treatment that can be used to reduce the burden associated with depression and anxiety disorders now.

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Toward precision medicine for depression: admitting ignorance and focusing on failures

I first recognized what R. Perlis¹ calls “artisanal practice” as a medical student in Liberia. Witch doctors – basically *the* local primary and psychiatric care providers at the time – regularly engaged in “throwing the bones”. Chicken bones, often in a bag but sometimes in hand, were shaken and thrown on the ground, resulting in a unique pattern which served as the basis for recommendation(s) offered to each “patient”. “Throwing the bones” was common and well accepted. So much so that it was rare to have dehydrated neonates arrive at the hospital without dung spread over their depressed

fontanelles, courtesy of the “doctor”. Personalized care – maybe; precision medicine – not so much.

But let me also defend some important aspects of personalized care. Organizing treatment steps based on reasonable Hippocratic principles and logic is appropriate². Avoiding medications that lower seizure thresholds in patients at risk, especially when safer options exist, is smart. My guess is that maybe 7-15% of depressed patients should avoid certain medications for medical reasons. In sum, let’s recognize that we too are throwing the bones when selecting among

antidepressant medications for specific patients, while we avoid certain treatments in selected patients for safety reasons.

To advance the precision of treatment selection, I agree with Perlis that we must provide systematic patient education, become adroit in the implementation of measurement-based care (to enhance efficacy and tolerability, and to reduce variations that interfere with signal detection) and shed our information about how to choose among treatments. Let’s leave the bones in the bag! We desperately need more knowledge about