Treatment-resistant depression:

clarifications and important steps forward

Eiko I. Fried, Ph.D.

University of Amsterdam

@EikoFried

http://eiko-fried.com

Adam M. Chekroud, MSc.

Yale University

@itschekkers

http://psychology.yale.edu/people/adam-chekroud

Introduction

The largest and longest investigation of treatment-resistant depression (TRD) to date, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), was conducted in four stages. Each stage comprised a different medication, and patients moved to the next stage if they did not improve considerably. Only 25% of all depressed patients remitted in stage I, only 46% after all stages [1]. TRD is a common and severe mental health issue, and research has shown that it is associated with worse outcomes and predicts lack of future treatment response: only 1 in 10 patients respond to standard treatments within 1 year [2].

In a recent article entitled "Toward an Evidence-Based, Operational Definition of Treatment-Resistant Depression", Conway et al. 2017 [2] convincingly argue that TRD is ill-defined. This imprecise definition, encompassing patients ranging from 1 to 8 failed

antidepressant trials, allows for substantial differences among patients categorized as treatment-resistant, and "limits the ability to do comparative treatment research [and] to understand the biological underpinnings of TRD". The authors call for a staging model in which they split TRD into two categories: patients with 2 failed trials vs. 3 or more failed trials. We agree that such a stage-based model borrowed from other areas of medicine could bring much needed clarity. The general approach of beginning with minimally invasive treatments (e.g. better-tolerated antidepressants, or psychotherapies), and gradually escalating through more invasive treatments as the patient does not achieve adequate response is already commonplace and recommended [3].

Two important considerations remain unaddressed by Conway et al. 2017. First, how useful is the category TRD in general? Second, how can we improve treatment outcomes in TRD: how do we prevent patients becoming treatment resistant in the first place?

Depression heterogeneity

Any medical subcategory can only ever be as useful as the category it is derived from. TRD defines a subpopulation of patients diagnosed with Major Depression (MD), a category that suffers from a lack of reliability and validity. The DSM-5 field trials identified MD as one of the least reliable diagnosis, with a kappa coefficient of 0.28 (on a scale from 0 to 1). MD does not compare well to other mental disorders in terms of meeting orthodox criteria for validity [4], defined as a clear clinical picture and/or etiology, clear boundaries to other disorders, treatment specificity, and temporal diagnostic stability. MD provides little information about the future course of illness, and efforts to identify consistent and reliable biological markers have failed. MD is also a highly heterogeneous disorder: 3,703 patients enrolled in STAR*D had 1,030 unique depression symptom profiles [5], and the most common rating scales for depression feature over 50 different symptoms [6].

More than 1 in 5 people will be diagnosed with MD in their lives, and many of these episodes differ considerably from each other. Susan loses her spouse, and with loneliness and insomnia come other symptoms. Mustafah breaks his leg and develops a chain of symptoms, starting with pain → sleep problems → fatigue → concentration problems, that lead to a diagnosis. Some people are stuck in life situations they cannot escape: an abusive relationship, a highly stressful job, or chronic unemployment. Others have had traumatic early life experiences, and/or dispositions for negative affect, rumination, or low energy. MD has many different faces [5], and there are as many reasons why depressed patients do not respond to treatment. This heterogeneity is a crucial limitation for the definition of TRD, and Conway et al. [2] rightfully suggest that the investigation of treatment-resistant depression*s* is a crucial step forward.

Multivariate prediction of TRD

Using data from the STAR*D trial, Perlis [7] described a retrospective model to estimate the risk that a patient would fail all four stages of treatment in the trial. This offers the possibility to use predictive models to determine whether a patient is likely to fail the traditional progression of treatments — before they have become treatment resistant. What if these patients were "fast-tracked" through traditional stepped care models? Early efforts are already underway to explore the possibility of placing patients immediately into high-intensity therapy if they have a poor prognosis, for example in the Improving Access to Psychological Care [IAPT] program in the U.K. [8].

Better matching of treatments to symptom profiles might further improve response rates in the context of TRD. As Conway et al. noted, TRD patients are characterized by lower productivity and higher suicidal ideation. However, recent findings from our group indicate that these are exactly the types of symptoms that respond poorly to antidepressant medications

in general [9]. Identifying those aspects of a patient's symptom profile that inform the likely outcomes of treatment before the treatment is selected might substantially improve treatment outcome for depressed patients.

The use of predictive tools in psychiatry is only nascent, and is in dire need of prospective randomized evidence that these approaches can improve outcomes. Efforts in the field might be better spent testing hypotheses and developing evidence to improve the wellbeing of patients than historic focuses on definitions and categories.

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