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EDITORIAL

Moving forward: how depression heterogeneity hinders progress in treatment and research

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1. Introduction

Few would argue that depression research in the last two decades has led to major improvements of clinical care for patients. The tools and insights we have at our disposal today have not changed much over the years. Three examples for slow progress are antidepressants, depression assessment, and research on biological markers. Drugs most commonly prescribed for major depression disorder (MDD) were developed in the 1980s and 1990s, only slightly outperform placebos, and their exact mechanisms remain unknown [1]. Hamilton's rating scale for depression – still the gold standard in clinical trials – is nearly 60 years old [2] and differs considerably from the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (DSM-5) MDD criteria [3]. And the study of MDD biology has largely resulted in null-findings or small effects that are impracticable for clinical purposes, despite ever-growing samples [4,5].

A growing chorus of voices – including prominent members of the DSM-5 task force and the National Institute of Mental Health (NIMH) [6,7] – has raised concerns about the reliability and validity of MDD, concluding that the clinical phenotype may hold little usefulness for research [8,9]. What exactly are the problems, and what can we do better?

2. Depression sum-scores don't add up

Nearly all depression research comprises several steps. A specific rating scale or clinical interview is selected among a large number of instruments [10], and symptoms such as sad mood, worthlessness, suicidal ideation, weight gain or weight loss, insomnia or hypersomnia, psychomotor problems, anxiety, genital problems, paralysis, crying, hypochondriasis, and lack of insight are assessed [3]. These diverse symptoms are added up to one sum-score that represents depression severity, and a threshold on the sum-score is used to distinguish individuals with MDD from healthy controls. Researchers then investigate whether variables of interest such as biological markers or treatment response are statistically related to the sum-score or compare patients and controls regarding such variables. Three lines of research demonstrate that this approach may obfuscate insights and hinder progress.

First, MDD is a highly heterogeneous diagnosis, and two patients with a DSM-5 diagnosis may share no single symptom. Alice comes into the practice as 10-am appointment reporting sadness, weight loss, psychomotor retardation, concentration problems, and suicidal ideation. Bob – our 11-am appointment – suffers from anhedonia, insomnia, self-blame, fatigue, and weight gain. A recent paper identified 1030 unique symptom profiles in 3703 depressed patients [11], and it seems questionable to investigate risk factors, biological markers, or other variables of interest in a depressed population when patients differ so considerably in their problems.

Second, it is remarkable how fuzzy the definition of MDD is. The most common rating scales feature over 50 disparate depressive symptoms [3], and many scales show little content overlap with the DSM-5 MDD criteria. Such a situation is difficult to envision for medical conditions like cancer or measles. The lack of a clear definition is also apparent in the fact that many different scales exist that aim to measure the same disorder – Santor et al. counted 280 different depression scales [10]. Moreover, dozens of MDD subtypes have been proposed and disregarded over the last century.

Third, the approach of summing disparate symptoms presupposes that all symptoms measure the same underlying construct, the same way that 10 math questions measure the same underlying construct 'mathematical intelligence' or 10 symptoms of cancer indicate the same underlying condition cancer. For depression, the notion that one sum-score of symptoms is a good proxy for severity is inconsistent with half a century of psychometric literature: depression rating scales are not unidimensional, a psychometric fact that cannot properly be reflected in one sum-score [12]. Nearly 60 years ago, Hamilton insisted in his seminal 1960 paper that the sum-score be regarded only as 'total crude score.' His case report of seven patients provides detailed information on four depression factors such as retarded depression and anxiety reaction, omitting information on the total crude score of patients that carries little information [2].

In sum, lumping disparate symptoms to a sum-score – and lumping patients with very different symptoms into one category – results in loss of important information. These common research practices have contributed to the lack of progress in depression research.

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3. Moving forward: Depression Symptomics

The novel research framework Depression Symptomics promises a way forward. Depression Symptomics aims to tackle widely acknowledged shortcomings of sum-scores and depression diagnosis by focusing on three objectives: studying (1) individual symptoms, (2) the causal relations among symptoms, and (3) personalized processes of patients.

3.1. Studying individual symptoms

Recent work has shown that specific MDD symptoms differ from each other in crucial aspects: They differ in their impact on impairment of functioning, their response to specific life events, their relations with biological markers, and their risk factors [13,14]. There is also evidence that symptoms differ in their response to antidepressant treatment [15,16] – which makes sense when we consider that the most common side effects of antidepressants are the very symptoms used to measure depression (e.g. fatigue, insomnia or hypersomnia, weight and appetite changes, and sexual dysfunction). When investigating changes of symptom sum-scores over time in clinical trials, patients' improvement on some symptoms is likely concealed by increases in other symptoms.

This also suggests that symptom-based investigations may offer potential for genetic and neuroimaging studies that have largely resulted in null-findings. The same holds for clinical trials: We should study what specific symptoms improve and worsen in response to specific antidepressants. This may enable us to predict based on baseline symptom profiles which participants will likely respond positively to what kind of drug. Many prior studies have investigated the efficacy of antidepressants, and while it is not always easy to obtain such data [17], we should try to utilize the already existing information for symptom-based investigations before we collect new data (cf. [15]).

3.2. Studying associations among symptoms

Symptoms of depression can interact with each other in complex dynamical systems, such as sadness → insomnia → fatigue → concentration problems. It is widely acknowledged that depressed patients are often trapped in situations of reinforcing problems. Such causal influences among symptoms are ignored in the study of sum-scores and have recently become a topic of detailed study in an emerging field termed 'network approach to psychopathology' [18,19].

Specifically, studies have shown that certain depression symptoms seem to be more relevant than others in symptom networks of patients, that symptom networks of depressed people show different characteristics than those of controls, and that symptom networks may emit so-called 'early warning signals' before healthy people transition into depression (review [18]). This network approach opens up new possibilities of timely prevention and intervention.

3.3. Personalized medicine

Recent technological developments such as smart-watches and other wearable devices allow for daily monitoring of depressed patients [20], and new statistical models enable us to estimate idiographic and nomothetic processes at the same time [21]. Personalized medicine – paying closer attention to differences among patients – may offer an important inroad to overcome limitations of the highly heterogeneous depression phenotype. Different fields of application come to mind: Improved prediction of depression onset in samples at risk of developing depression, improved prediction of depression relapse, and improved prediction of treatment [22].

3.4. The clinical utility of Depression Symptomics

Depression Symptomics is a novel research framework that has led to important scientific insights in different domains of research – but does it offer therapeutic gain for patients? There are several studies in support of this notion. Regarding (1) studying individual symptoms, MDD symptoms differentially predict relapse [22] and differ in their responsiveness to treatment both within and across different antidepressant medications [15,16]. Regarding (2) studying associations among symptoms, symptoms that drive depressive processes seem to be especially strong predictors for future depression [23] and so are depression networks where symptoms are strongly interconnected [24]. For (3) personalized medicine, a randomized clinical trial has shown that providing patients with idiographic feedback about their dynamic processes leads to a reduction of depressive symptomatology [25], and a study with one participant was able to predict the relapse into depression before it occurred based on a complex dynamical systems model [26].

4. Future outlook

MDD diagnosis provides little clinical utility: It lacks treatment specificity, a clear clinical presentation, and precise diagnostic boundaries and has high comorbidity rates and a very low inter-rater reliability [8,9]. Head of the DSM-5 task force David Kupfer concluded that 'the relatively low reliability of major depressive disorder […] is a concern for clinical decision-making' [6], and prior NIMH director Thomas Insel stated that the DSM's main weakness is its 'lack of validity' [7].

Depression Symptomics conceptualizes individual symptoms as fundamental building blocks of mental disorders that provide an untapped source of important and clinically relevant information. This is consistent with the NIMH strategic plan for mood disorder research and the NIMH Research Domain Criteria that aim to study and identify more homogeneous and reliable endophenotypes [7,27]. Embracing complexity was a key requirement to recent insights in biology, economics, and environmental sciences, and Depression Symptomics may change our perspective of MDD from an unwieldy and cumbersome disorder to a phenotype where attention to specific symptoms and their interactions – and attention to differences between patients – are crucial for scientific and clinical progress.

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Declaration of interest

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