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Unpacking Major Depressive Disorder: From Classification to Treatment Selection

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In the past decade, there has been a revival of the debate about diagnostic approaches in mental illness. In 1970, Robins and Guze[1] described 5 distinct requirements to justify the diagnosis of a psychiatric syndrome. These involved 1) a consistent clustering of symptoms, 2) laboratory studies to establish a biological substrate, 3) relative specificity of symptoms to distinguish one disorder from another, 4) evidence from follow-up studies of a common course of illness, and 5) some evidence of genetic predisposition based on higher prevalence rates in the families of affected individuals. There are many potential benefits to this approach: internationally accepted taxonomy facilitates studies across multiple research areas, ranging from epidemiology and health economics to disease mechanisms, treatment outcome evaluations, and pursuit of new therapeutics.

On the other hand, major depressive disorder (MDD) is a prime example of the limited success of this 'one-size-fits-all' approach, where less than 30% of individuals achieve remission during a first observed antidepressant trial.[2] This not only increases the burden of functional impairment across domains of occupation, physical health, and social relationships[3] but also contributes to the unwelcome position of MDD as the leading cause of disability worldwide.[4] Using current criteria in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), more than 200 combinations of symptoms may be applied to fulfill the diagnosis of a major depressive episode (MDE), highlighting the significant clinical heterogeneity of the disorder.[5,6] Even when MDD is classified according to symptom clusters (e.g., melancholic, atypical, and anxious), these clinical phenotypes have not proven useful as predictors of antidepressant outcome and, by implication, treatment selection.[7] How can we do better?

The answer may lie in precision medicine, integrating clinical and biological measures that are unique to the individual to select the best treatment while minimizing adverse effects. Biomarkers promise better diagnostic methods and treatment selection—and rather than being unique to any specific *DSM* disorder, these biomarkers may transcend traditional diagnostic boundaries. The Research Domain Criteria (RDoC) framework, proposed by Insel et al.[8] at the National Institute of Mental Health (NIMH), is agnostic to *DSM* disorders and proposes an integrated dimensional approach to understanding psychiatric disorders by incorporating data from various modalities on a continuum of human behaviour from normal to abnormal. While RDoC is still in its preliminary stages and has not yet influenced clinical practice, the ability to cut across traditional diagnostic boundaries may prove useful for future conceptualization of disorders. This 'lumping' and 'splitting' of diagnoses has resulted in significant progress in the treatment of many cancers and immune disorders, with classifications and treatment strategies being guided by underlying biological mechanisms rather than surface clinical manifestations. Although the RDoC model is intended as a framework for conducting research rather than a diagnostic system, it may be useful in representing overlapping phenotypes across disorders, as well as heterogeneity within disorders such as MDD. Indeed, while evidence of phenotypic heterogeneity in MDD can be observed clinically, the full extent of its variability likely spans all RDoC units of analysis, from

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genes, molecules, and cells to brain circuits, physiology, and behaviour.

Network Disturbances

At the brain circuit level, altered network activity at rest has been explored as a potential biomarker for predicting treatment outcomes. In one example, four distinct MDD neurophysiological 'biotypes', characterized by distinct patterns of limbic and frontostriatal functional connectivity, were defined using functional magnetic resonance imaging (fMRI). These biotypes were associated with distinct profiles of clinical symptoms; for example, biotype 1, which responded best to repetitive transcranial magnetic stimulation (rTMS) therapy, was associated with high levels of fatigue and low anhedonia.[9] In a separate example, using both positron emission tomography and fMRI, baseline moderators of response to either escitalopram or cognitive behavioural therapy (CBT) were identified: levels of glucose metabolism in the right anterior insula and functional connectivity of the subcallosal cingulate cortex were strong predictors of remission or nonresponse.[10,11] Importantly, these two studies represent a replication of findings using different functional imaging modalities, strengthening the notion of the insula and subcallosal cingulate as key imaging markers for treatment selection.

Toward a 'Liquid Biopsy' for MDD

A perceived impediment to the biomarker approach in depression and other psychiatric disorders has been an inability to access tissue samples, as in cancer and other diseases where most advances in precision medicine have occurred.[12] However, the recent utility of circulating cancer biomarkers such as blood-borne microRNAs (miRNAs) to identify early metastatic spread[13] validates the potential of 'liquid biopsies'. This is very relevant to molecular studies in MDD, where changes in circulating miRNAs, regulatory enzymes, and inflammatory cytokines have been associated with treatment outcomes.[14,15] Lopez et al.[16] recently identified 3 miRNAs that were differentially expressed according to duloxetine treatment response. Glycogen synthase kinase 3β (GSK3β), an enzyme associated with neurogenesis and regulated by monoamines associated with MDD, has also been investigated as a predictor of antidepressant response.[17] In addition, there is a growing interest in inflammatory cytokines as markers of disease state and treatment outcome. For instance, a recent study of the tumour necrosis factor (TNF) antagonist, infliximab, in a treatment-resistant depression (TRD) sample demonstrated treatment efficacy only in individuals with high inflammatory markers at baseline,[18] and recent data suggest that elevated C-reactive protein (CRP) levels in combination with altered hypothalamic-pituitary-adrenal (HPA) axis activity may differentiate unipolar and bipolar depression in men.[19]

Refining Clinical Phenotypes of MDD

Alongside the quest to identify biomarkers through neuroimaging and 'liquid biopsies', more nuanced behavioural and self-report measures may also prove useful in refining clinical phenotypes of MDD. While the heterogeneity of the disorder is clear, identifying homogeneous subgroups that respond to treatment in similar ways is substantially more challenging. Individual depressive symptoms differ in their contributions to overall functional impairment, with sad mood, concentration difficulties, fatigue, and anhedonia having the greatest weights.[20] In current practice, treatment selection may be guided by the Canadian Network for Mood and Anxiety Treatments (CANMAT) recommendations,[3] which suggest additional clinical specifiers above and beyond those included in the *DSM*. Greater attention to individual symptoms such as sleep disturbance, cognition, and anhedonia may assist with illness characterization and treatment selection, as different antidepressant medications are known to exert differential effects on these specific symptoms. Examples include the work of Rush et al.[21,22] and Chekroud et al.[23], who replicated 3 symptom clusters—core emotional, atypical, and sleep/insomnia—in 3 large data sets (Sequenced Treatment Alternatives to Relieve Depression [STAR*D][21], Combining Medications to Enhance Depression Outcomes [CO-MED][22] and 7 randomized placebo-controlled trials of duloxetine[23]). In this study, the most prominent antidepressant effect was on the emotional symptom cluster, followed by the sleep cluster, with less effect on atypical symptoms. In addition to pharmacological approaches, it is also important to recognize that CBT has proven to be equally effective in achieving response and remission compared to antidepressant medications in a large meta-analysis,[24,25] although it is currently unclear whether attention to specific symptoms may reliably predict response to psychotherapy.

Sleep and Alertness

Within a clinical sample, sleep disturbances have been reported in 85% of individuals in a current MDE[26] and may take the form of either insomnia or hypersomnia. Commonly used scales to assess sleep within the context of MDD include the Pittsburgh Sleep Quality Index (PSQI),[27] as well as individual items on standard depression scales such as the Hamilton Rating Scale for Depression (HRSD).[28] Several studies have found associations between sleep disturbances and poor treatment outcome with both psychotherapy and pharmacotherapy.[29-32] In the context of treatment selection, mirtazapine may be chosen in individuals with sleep disturbances for its sedating effect, whereas bupropion may be selected to increase alertness and motivation.[33]

Cognitive Deficits

Cognitive symptoms have been reported in 94% of individuals in a current MDE and were found to persist during

remission in 44% of cases.[26] Specifically, difficulties with concentration and decision making were identified in a recent systematic review as being among the most burdensome symptoms in MDD.[34] It is important to target cognitive symptoms as well as mood symptoms when treating these individuals to maximize functional outcomes. To this end, treatment with vortioxetine, bupropion, or duloxetine in MDD patients with marked cognitive dysfunction may be among the most suitable choices, according to evidence-based guidelines,[33] and delayed recall and psychomotor speed may be facets of cognition that are improved most significantly with antidepressant treatment.[35]

Anhedonia

Clinically significant levels of anhedonia have been reported in 37% of individuals in an MDD sample[36] and represent significant functional burden.[37] Several scales have been designed to assess this core symptom of MDD, including the Snaith-Hamilton Pleasure Scale (SHAPS)[38] and the Dimensional Anhedonia Rating Scale (DARS).[39] These scales probe multiple facets of response to reward, including loss of interest, motivation, and pleasure, and can provide substantially more insight into the symptom than a single criterion as found in the *DSM* or the HRSD. The depth and sensitivity of these measures may allow for their utility in treatment selection; for instance, the DARS has demonstrated preliminary utility in distinguishing between treatment-resistant depression (TRD) and non-TRD subgroups.[39]

The individual clinical features outlined above may have genetic and neural underpinnings that span multiple RDoC units of analysis, permitting a more integrative approach to the study of these specifiers. Revisiting the example of anhedonia, this clinical phenotype can be viewed as a transdiagnostic manifestation of dysfunction at multiple levels of analysis,[40] from self-report measures of diminished interest and pleasure, to behavioural tasks probing various aspects of reward function, to differences in brain activation in response to reward or punishment stimuli.[41-43] These findings, either alone or in combination, may have implications for predicting illness onset and outcome. This has been shown in adolescent samples, whereby decreased striatal activation during reward anticipation was associated with increases in depressive symptoms over 2 years.[44] At the level of treatment selection, responders to rTMS to the dorsomedial prefrontal cortex were shown to have preserved hedonic function, while nonresponders had baseline anhedonia and abnormal connectivity in brain reward circuitry.[45] It is important to recognize, however, that most of the indicators identified thus far within personalized medicine in psychiatry are negative prognostic factors that can identify which treatments will be met with *poor* response, rather than positive factors that can guide treatment personalization by identifying interventions that will be particularly effective for the individual.[46,47]

Next Steps in Precision Medicine and The Rise of 'Big Data'

What does the future look like for precision medicine in psychiatry? The world of 'big data' has significant appeal, and sophisticated machine learning techniques may represent the next step in integrating basic and clinical data. In addition to the face-to-face assessments that have been a pillar of psychiatric assessment, there is now also a growing interest in emerging mobile health (m-Health) technologies, which may support a more direct, albeit remote, assessment of symptoms and real-world functioning. Ecological momentary assessment (EMA) through smartphones or wearables provides the opportunity for real-time assessment of function using noninvasive technology with primarily passive data collection. With the expanding role of technology in daily life, the notion of a 'digital phenotype' based on measures of interaction with technology is being explored as a potential mechanism for identification and surveillance of health conditions.[48,49] For instance, global positioning systems (GPS) data and measures of smartphone usage such as duration and frequency have been used to predict depression symptom severity.[50] In addition to symptom monitoring, m-Health may also be used for widespread delivery of targeted interventions, with the advantage of being accessible from remote locations. Internet-based CBT has increased in popularity as an alternative means of delivering psychotherapy, with one study reporting similar efficacy to face-to-face intervention.[51] Furthermore, one proof-of-concept study reported improvements in cognitive control in late-life depression following a therapeutic video game intervention.[52] Even with these more sophisticated methods of measurement and treatment delivery, it is clear that 'not all depressions are created equal' and one measurement or treatment approach may not be suitable for everyone; individual MDEs may represent different proportions of biological, psychological, and situational factors. Thus, consideration of additional factors beyond clinical and passively collected physiological markers alone may be necessary in many cases for optimizing treatment selection, and early imaging and molecular studies have shown promise.

The ultimate goal, then, is to integrate data across modalities in a way that is clinically meaningful and feasible for translation into clinical practice. The resulting phenotypes may be useful to (a) predict response to currently available treatments and (b) build upon to identify more specific targets for novel interventions. As we have discussed here, recent advances in precision medicine for MDD are encouraging; however, current progress is hindered by 'failure to replicate' and relatively small sample sizes, highlighting the urgency for new groups using newer 'big data' approaches to integrate findings across studies and modalities. Large multisite collaborative studies such as the International Study to Predict Optimized Treatment for Depression (iSPOT-D),[53] the Genome-based Therapeutic Drugs for Depression (GENDEP) project,[54] the STAR*D study,[55] and the

Canadian Biomarker Integration Network in Depression (CAN-BIND)[56] have produced rich data sets that explore various aspects of heterogeneity from pharmacogenetics to inadequate treatment response, and allow for integration across modalities in line with a dimensional approach. New sophisticated machine-learning algorithms[57,58] may be applied to these data to better classify individuals by taking into account multiple measures that span clinical, genetic, molecular, and/or imaging platforms. In true RDoC fashion, the next step should be to look cross-diagnostically at domains of function or dysfunction rather than constraining within our current diagnostic system. This reflects the aspiration of Herman Van Praag et al.,[59] who surmised in 1990 that 'once correlations between psychological and biological dysfunctions have been established, the next step inevitably will be the search for drugs that can selectively correct the biological dysfunctions ... irrespective of nosological diagnosis'. Nearly three decades have passed since the comment by Van Praag et al., and while significant progress has been made, it may take several decades more before we achieve true 'precision psychiatry'.

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