Primed for Psychiatry: The role of artificial intelligence and machine learning in the optimization of depression treatment

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Abstract

Depression is a leading source of medical disability and is experienced by over 322 million people worldwide. Despite its increasingly significant burden and a pressing need for effective treatment, depression has been persistently difficult to treat. Current common practice for treatment selection is an educated guess-and-check approach, in which clinicians prescribe one of the numerous approved therapies for depression in a stepwise manner. Though evidence-based clinical guidelines for managing depression exist, there is a paucity of evidence to support specific treatment recommendations. A significant barrier to developing such recommendations is the symptom heterogeneity present in the diagnosis of major depressive disorder. Machine learning offers the ability to recognize this heterogeneity and model that information in psychiatric disorders. Specifically, machine learning allows processing of high-dimensional data, the management of missing data, creating high-level abstractions, and the freedom of not requiring *a priori* patient stratification. While ethical concerns arise in employing these methods, the benefits are wide-reaching, from personalizing treatment for depression, to the development of artificial intelligence chats that employ psychotherapy, to predicting social outcomes for patients with mental illness. The implications extend far beyond depression treatment, as the epidemiology and service demand for mental healthcare systems continue to grow. Indeed, psychiatry is primed for innovation in artificial intelligence and machine learning.

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Part I: The State of the Field

Major Depressive Disorder: The Burden of Disease

Depression is a leading source of medical disability and is experienced by over 322 million people worldwide.[1] Though prevalence rates vary by sex and age, the average 12-month prevalence of depression is approximately 6%, with a lifetime prevalence estimated to affect one in every six adults.[2] The medical burden of depression extends to somatic health, increasing the risk for cardiovascular disease, diabetes, and all-cause mortality.[3] Further, rates of depression are rising with increasing rapidity. Between 2005 and 2015, the World Health Organization found an 18.4% increase in depression prevalence.[1] American health insurer BlueCross BlueShield, which covers 41 million people, reports a 33% increase in depression diagnoses from 2013 to 2016 in both men and women.[4] Whether a higher proportion of individuals are experiencing depression or more diagnoses are being made, the fact remains that our healthcare systems are facing an unprecedented number of patients requiring treatment for depression.

Treating Depression: Where Psychiatry Falls Short

Despite its increasingly significant burden and a pressing need for widespread treatment, depression has been persistently difficult to treat. Indeed, in the largest clinical trial of depression treatment, the National Institute of Mental Health-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the authors observed that nearly 70% of patients failed to remit after their first course of treatment. After four treatment attempts totaling nearly a year, 30-40% of patients did not recover from their depression.[5,6] Even among those who remit, residual symptoms, such as comorbid anxiety conditions and impaired long-term functioning may persist.[7]

While response rates to antidepressants are suboptimal, they are generally reported as superior to placebo[8] and remain the most common first-line treatment strategy, though numerous psychological and alternative treatment options exist.[9] Evidence-based clinical guidelines for the treatment of depression, such as the Canadian Network for Mood and Anxiety Treatments (CANMAT), outline recommendations for the management of major depressive disorder (MDD).[10] Current common practice for treatment selection is an educated guess-and-check approach, in which clinicians prescribe one of the numerous approved therapies for depression in a stepwise manner.[10,11] A common approach is to test a class of medication for 2-4 weeks before assessing remission response.[10] In the event of minimal clinical improvement, another medication, either within the original class or in a different class, is trialed for 2-4 weeks.[10] Alternatively, some clinical improvement may be achieved. In this scenario, the dose of the initial antidepressant should be increased if this is tolerable to the patient. If increasing the dose does not improve symptoms, another medication may be added to either augment or combine with the existing treatment.[10] However, if the response to first-line antidepressant treatment is inadequate, most clinical practice guidelines do not provide specific suggestions for choosing an alternative antidepressant.[12] A recent systematic review and network meta-analysis demonstrated that clinical efficacy is not statistically different among 21 common antidepressants.[13] As a result, clinicians resort to making decisions based on an educated guess-and-check approach, which may be informed by patient factors such as genetic susceptibility, family history, and medical comorbidities.[10] There have been recent calls for the need of increased measurement-based care (MBC) in psychiatry,[14] the practice of using routine patient-reported symptom measurement to inform clinical decision making. Though it is well-established that MBC is beneficial to primary care for depression,[15] it is rarely implemented due to challenges with time efficiency and integrating this practice into the clinical workflow.[16]

There are numerous shortcomings of conventional psychiatry in providing effective treatment for patients with depression. First, depression is a chronic condition, characterized by multiple episodes and relapses, although it is often treated acutely. Second, the most commonly prescribed treatment option, antidepressants, is more effective than placebo, but these effect sizes are modest,[13] and the burden of side effects can outweigh the benefits for some patients. Thirdly, a considerable barrier to effective treatment of depression lies in the heterogeneity of symptoms and complex etiology and progression of the disorder. The current classification system for depression is based on a range of symptoms encompassing their extremes. Indeed, the DSM-V diagnostic criteria for MDD include either considerable weight gain or weight loss, increase or decrease in appetite, insomnia or hypersomnia, and psychomotor agitation or retardation.[17] Two individuals presenting with contrasting clinical profiles might receive the same diagnosis of MDD. One study identified 119 different depressive symptom combinations that all fit under the umbrella of MDD.[18] The failure to stratify clinical populations in depression, along with the inadequacies of traditional statistics to capture this patient heterogeneity might explain the inconsistency of findings in extant literature on the pathophysiology of depression,[19] as well as the disproportionately large failure of psychiatric drugs in late-stage clinical trials, compared to other disease areas.[20]

Part II: The Application of Machine Learning to Achieve Personalised Treatment in Psychiatry

Introduction to machine learning methods

Techniques in machine learning comprise a spectrum of statistical methods to model complicated interactions between variables in large and heterogeneous datasets, coined 'big data'.

In contrast to the limitations of traditional statistical methods to model the symptom heterogeneity of depression and other psychiatric illnesses, machine learning offers the ability to recognize patterns (i.e., relationship between symptom profile and treatment response) among complex, multimodal, unstructured datasets.[21-23] Deep learning is a subset of machine learning methods capable of modelling the relationship between inputs and outputs of interest through the use of multiple 'layers' of a neural network.[24] These layers are inspired by knowledge from biological neural systems that neurons communicate and encode information through an interconnected network in which each neuron integrates chemical or electrical inputs from neighbouring neurons and propagates the output to other neurons if the weighted sum of the inputs exceeds a certain threshold. As the algorithm trains on target examples, multiple layers of artificial neurons, or 'nodes', allow the model to learn relationships between input and output, and iteratively adjust connection weights between nodes. In the case of depression, the outputs of a neural network model could be diagnostic classification or treatment response, and inputs could be patient information at the level of demographics, symptom profile, neuroimaging markers, cytokine or metabolite levels, genetics, proteomics, measures from cognitive tests, or the combination of all of the above.[25] Due to the multiple layers of neural networks involved in learning the relationship between inputs and desired output, deep learning is especially well-suited for predicting future outputs, such as treatment response, from past inputs (e.g., age of onset, interleukin concentration, or score on a questionnaire assessing symptom severity). We will now discuss the specific aspects of deep learning that make it useful for handling the complexity, multimodality, and heterogeneity of data available for understanding mental illness.

Advantages of Deep Learning for Modeling Heterogeneity and Complexity in Psychiatric Disorders

1) Ability to Process High-Dimensional Data

High-dimensionality in machine learning refers to datasets with large numbers of variables or dimensions, which interact in different ways to form high numbers of clusters or high dimensional spaces. To illustrate, mood disorders are complex and associated with multiple levels of explanation, from childhood upbringing, to the genetic composition of an individual, to the structure and function of their brain, to the functioning of their immune system, to their current diet, lifestyle, age, and somatic health. To understand the neurobiological underpinnings of psychiatric illness, many different types of variables or features are collected from large numbers of individuals, resulting in datasets containing information on large volumes of variables for a large volume of people. Here, deep learning is especially relevant as it uses "hidden" layers to overcome the increasing number of multimodal interactions by computing intermediate outputs that are not necessarily visible to the user.

2) Ability to Manage Missing Data

Pooling aggregate data to analyze with machine learning techniques often leads to incongruous features collected between different datasets. Data in psychiatry is particularly subject to missing data as patients with psychiatric disorders often show high attrition rates in clinical trials, may be unreliable in attending appointments or recording self-reported information, and may be non-compliant to treatment adherence. Fortunately, there are strategies that serve to overcome the challenge of missing data, such as imputing the missing entries and proceeding as though the imputed values are true values.[26,27]

3) Creates High-Level Abstractions of Data

The multiple layers and iterative nature of deep learning in changing the weights of its connections allows the model to create increasingly complex and abstract representations of the input data. Abstraction can reduce the complexity of a representation while preserving important features. This aspect of deep learning is pertinent to model psychiatric illnesses, which are inherently complex in their etiology.

4) Does Not Require *a Priori* Patient Stratification

In applying traditional statistical methods, researchers sometimes stratify patients based on different features, such as severity of depressive symptomatology or age of onset of illness, and relate these to outcome measures like treatment response. However, there may be other stratification classes that are more relevant to predicting treatment response. Since deep learning does not require the input data to be stratified in any way, models may be considered agnostic to the underlying pathophysiology of a pertinent disease.

5) Does Not Depend on Manual Feature Engineering

Unlike other machine learning techniques that require manual input of select feature sets, deep learning based algorithms can identify the input features that are most salient in mapping to a desired output. Thus, no *a priori* information is required concerning which input features might be important towards making a diagnostic or treatment classification decision. *A priori* knowledge may still help, however, in reducing the number of features to be processed by a model, though it also often introduces potential bias.

Limitations and Ethical Concerns of Using Machine Learning Methods in Psychiatry Research

Machine learning has many advantages over traditional statistical techniques, which makes it useful for modeling data on psychiatric disorders. However, its promise comes paired with practice and ethical challenges of applying deep learning to big data analytics for psychiatry. Practically, deep learning requires volumes of data to sufficiently teach an algorithm the relationships between inputs and the target output, which can be challenging to amass. Even with sufficient data, underrepresentation of minority groups may limit the generalizability of results. Though there are strategies to overcome such limitations, the ubiquity of missing data can introduce bias into the dataset. Conceptually, since deep learning contains many hidden layers, of which intermediate computations we are not necessarily privy, deep learning models can function as "black boxes", delivering an output that cannot always be clearly traced back to a specific initial input. The concern here is whether the diagnostic classification or treatment decision of the algorithm is correct if we cannot trace the decision tree from which it originated. The degree of interpretability is in trade-off with the complexity of the model. However, interpretability is an area of research receiving increasing focus.

Part III: Select Review of Advances of Artificial Intelligence in Psychiatry Research

1) Deep Learning for Personalized Treatment of Depression

The poor treatment efficacy and lack of tailored treatments in depression (part I) underlines the urgent need for an evidence-based approach to select the best treatment option for a given patient presenting with symptoms of depression. Aifred Health, an IBM Watson AI XPRIZE team based in Montreal, Canada, is addressing this need by developing a deep-learning powered clinical decision tool to help physicians better tailor mental health treatment plans to each patient. Their approach entails training their deep learning model on large datasets of patients receiving treatment for depression containing rich information about sociodemographic factors, symptom profiles, neuroimaging markers, genetics data, and metabolic, endocrine, and immunological profiles. So far, the team has amassed critical datasets from clinical trials on pharmacotherapy, psychotherapy, and alternative treatments for depression for model training, validated their deep network, and is in the process of preparing interpretability of treatment recommendations by the clinical decision aid tool and producing protocols to engage the model in ease of use and randomized control trials.[28]

2) Artificial Intelligence for Psychotherapy

Psychotherapeutic interventions have similar efficacy rates compared to pharmacotherapy for depression treatment.[10] However, psychotherapy can be difficult to access for uninsured patients and wait times can be lengthy. Initiating face-to-face psychotherapy may not offer the timely support required by patients at the start of treatment. An artificial intelligence (AI)-enabled, text-based conversational mobile mental wellbeing app can bridge this gap. Wysa is an AI-powered coach that responds to the user's emotions by employing psychotherapy methods from cognitive behavioural therapy, dialectical behavioural therapy, meditation, breathing, yoga, motivational interviewing, and other resilience building skills.[29] One commenter mentioned that Wysa's technology responds so quickly to a user's emotions that the programmers had to program a few seconds delay to make the interaction seem more human.[29] Given the speed and accessibility of Wysa, 67.7% of a study of 129 users found the app experience helpful and encouraging.[29] Among a high user versus low user group (N = 108 vs. N = 21), the average mood improvement was significantly higher in the high user group compared to the low user group (mean = 5.84, standard deviation (SD) 6.66 vs. mean = 3.52, SD 6.15).[29]

3) Prediction of a Patient's Social Functioning

Predicting a patient's social functioning, such as their ability to create and maintain relationships, is pivotal in providing individualized social services as well as addressing chronic causes of disability. Researchers from Australia used machine learning to predict social outcomes of a group of 120 people aged 15–40 years experiencing recent onset depression.[30] Social outcomes were measured based on the person's ability to secure employment, complete education, maintain satisfying relationships, and achieve emotional equilibrium. By comparing how well machine learning can predict social outcomes versus human expert-based decisions, machine learning outperformed human experts by 70%.[30] Assessing how well an emerging adult will function socially in the future can lead to innovative preventative measures in the social determinants of health. Given the delicate onset of education, employment, relationships, and emotional satisfaction experienced during the young adult years, this study demonstrates the potential of AI in predicting social function.

Part IV: Beyond Depression: Targeting the General Burden of Mental Health and the Implications for Society

The implications of AI and machine learning in psychiatry extend far beyond improving outcomes for depression. Clinical treatment for most psychiatric conditions could also benefit from AI insights, including but not limited to psychosis, anxiety, substance use and addictions, and personality disorders.

Around 20% of all Canadians will experience mental illness in their lifetime.[31] Strikingly, the prevalence of untreated mental illnesses is remarkably high, with only one out of every five people reaching out for help.[31] It is cited that one of the greatest reasons for this lack of service utilization is the social stigmatization of mental illnesses.[31] The Centre for Mental Health and Addiction (CAMH), one of the largest psychiatric hospitals in Canada, launched an ambitious "Mental Health IS Health" public awareness campaign to illustrate the concerns that mental health is not taken as seriously, nor treated as urgently, as physical health.[32] It debunks the myth that mental health is not a legitimate health issue and has since been promoted on commercials, social media, public transit stops, as well as highway sign ads.[32]Campaigns such as the "Mental Health IS Health" movement are expected to decrease the stigmatization against mental illnesses and increase the demand for mental health services.

Applying AI to mental health is an opportunity to tackle one of society's greatest burdens. As social stigmatization decreases and help-seeking behaviour increases, they force our healthcare system to address the increased need for mental health services. Federal agendas have taken note, with the Mental Health Commission of Canada launching a report in 2014 to target innovation in eMental Health.[33] Priorities include an updated literature review and environmental scan of existing research, engaging people with lived experience, creating an evaluation framework for eMental Health apps, and sharing a toolkit for eMental Health implementation across Canada.[33] Goals include shortening wait times, reaching a broader geographical audience by improving accessibility in remote regions, having a cost-effective service delivery, and personalizing services to specific habits and genetics.[33]. Large advocacy bodies, such as the Canadian Psychiatric Association, also focused on eMental Health and AI in their 2018 Annual Conference.[34] Additionally, the Canadian Mental Health Association included knowledge exchange of eMental Health innovations at their Annual "Mental Health For All" conference in October 2018.[35] The momentum is only expected to grow and there is no better time for AI to thrive in the field of psychiatry.

Conclusion

Given the increasing burden of depression worldwide and a pressing need for treatment, AI and machine learning offer an alternative model for optimized treatment. Specifically, these modalities allow processing of high-dimensional data, the management of missing data, a creation of high-level abstractions, and the freedom of not requiring a priori patient stratification. The benefits include a personalized treatment for depression, the development of AI chats that employ psychotherapy, to predicting social outcomes for patients with mental illness. Future directions to refine the mathematics of these models and to tackle ethical considerations, such as the engagement of minority populations, will aid research in this field. Indeed, with the current trajectory of AI and machine learning, psychiatry is primed for innovation.

Conflict of Interest

D.B. and S.I. are shareholders of Aifred Health, a medical technology company that uses deep learning to increase treatment efficacy in psychiatry. C.R. received compensation from Aifred Health. J.T. declares no conflict of interest.

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