Can precision medicine advance psychiatry?

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Precision medicine is a new approach that considers differences in genes, environment, and lifestyle in an attempt to tailor treatments for individual patients. Psychiatry, as a discipline, has historically relied on clinical judgement and phenomenology-based diagnostic guidelines and has yet to take full advantage. This editorial provides an insight into the expanding role of precision medicine in psychiatry, both in research and clinical practice. It discusses the application of genetics and subgroup stratification in increasing response rates to therapeutic interventions, mainly focusing on major depressive disorder and schizophrenia. It presents an overview of machine learning techniques and how they are being integrated with traditional research methods within the field. In the context of these developments, while emphasizing the considerable potential for moving toward precision psychiatry, we also acknowledge the inherent challenges.

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Introduction

Personalized and precision medicine is at the forefront in modern healthcare. This may represent the dawn of a new way to think about and practice medicine, but what does it actually mean? Some of the concepts underlying personalized medicine have a long pedigree, but its modern father is generally considered to be Archibald Garrod, who practiced in the early 20th century (Perlman et al. 2016). Garrod mused that the job of a physician is not to blindly apply the knowledge they have acquired; it is to take differences into account in order to maximize benefits for each individual patient. A modern definition of personalized medicine is stated as, ‘an approach to disease treatment and prevention that considers individual differences in genes, environment, and lifestyle’ (Genetics Home Reference 2015).

Many researchers now prefer the term precision medicine to personalized medicine. This represents a clarification, as the word personalized tended to be misconstrued as providing completely individualized treatments for each patient, which is not the case. The National Research Council has pointed out that precision medicine ‘does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease . . . or in their response to a specific treatment’ (National Research Council 2011). While the term precision medicine is beginning to enter current medical parlance, ‘precision psychiatry’ will not come to mind for most health professionals, or for the public. Even within the medical world, precision medicine is commonly perceived as the domain of more technologically supported medical specialists, for example, oncologists who can now prescribe ‘magic bullet’ drugs such as Trastuzumab (Herceptin), used to treat HER2+ breast cancer, or Imatinib, the first-line treatment for Philadelphia chromosome-positive chronic myeloid leukemia (Maximiano et al. 2016; Sacha 2014).

To a large extent, this perception may be accurate. However, there is now an increasing opportunity for psychiatry, as a specialist discipline, to embrace precision psychiatry, thereby innovating how we diagnose and treat some of the most vulnerable people in our society. Here, we will review progress to date, consider how precision medicine approaches may improve specificity, how new technologies can complement existing approaches, and the potential challenges to the field.

The story thus far

How can precision medicine be integrated into psychiatry? Several developments, separately or in combination, are likely to contribute, from the use of genetic testing to improve patient selection for treatments to the introduction of deep-learning systems. Ozomaro and colleagues, for example, have reviewed the progress of precision medicine in major depressive disorder (MDD), bipolar disorder (BP), and schizophrenia (SZ) (Ozomaro et al. 2013). They describe how genetics and epigenetics influence the heritability of these diseases and their role in predicting treatment response. They included data analyzed by Apud et al., which studied the relationship between voltage-gated
potential improvements to clinical practice have been made with the commercial availability of pharmacogenetic-based decision-support tools. Some, such as GeneSight, have a growing evidence base to support their utility in guiding treatment choices for MDD, although these have yet enter widespread usage (Hall-Flavin et al. 2013; Winner et al. 2013). The National Institute for Mental Health (NIMH) has modified the Research Domain Criteria, aiming to integrate a wider range of information such as genomics and proteomics into the field of psychiatry, supplementing the phenomenology-based DSM and ICD criteria as the current cornerstones of clinical practice (Menke 2018). There has been considerable debate surrounding the introduction of the DSM 5, much of it surrounding a perceived over-medicalization of the normal range of psychological states and a lack of evidence validating the growing list of diagnoses (Pickersgill 2014). In the context of such inevitable controversy in regard to the enduring reliance on clinical judgement in psychiatric diagnosis, psychiatry should seek to maximize the use of tools we now associate with modern medicine, including biomarkers, imaging, genetic testing, and machine learning.

The benefits of specificity

One of the terms that repeatedly appears in the precision medicine literature is specificity. While psychiatrists are usually aware of a number of treatments that may work for a range of people, they can rarely predict which patients will respond to any individual option. This conventional, top-down approach generally results in trialing different treatments and evaluating the outcome clinically. Management strategies have improved dramatically over the years, but even in highly prevalent illnesses such as depression, over 50% of patients will be non-responders to their first-line medication (Boland et al. 2018; Trivedi et al. 2006). This can negatively impact the patient’s outlook on their illness and affect the doctor–patient relationship while also risking the development of an attitude of therapeutic nihilism. Any two patients may be assigned an identical diagnosis, but are likely to have distinct psychopathologies requiring different treatments, because psychiatric disorders involve multiple and varying psychosocial and neurobiological routes. By utilizing genomics, proteomics and other associated technological advances, it is possible to build more accurate models of the specific neurochemical abnormalities (Waddington et al. 2019). While precision psychiatry, therefore, will not be able to solve the problems of variable and unpredictable response to treatment entirely, the hope is that we can at least improve the odds.

Using the example of major depressive disorder (MDD), while we understand that neurotransmitters such as serotonin play an important role, it is clear that they do not explain the entire picture (Dell’Osso et al. 2016). Large cohorts of patients have limited or no response to first-line selective serotonin reuptake inhibitors (SSRIs), and while there are many proposed factors that influence response, we cannot identify those patients who will respond fully, partially, or not at all (El-Hage et al. 2013). Advances in precision psychiatry hope to address this challenge. Studies have shown, for example, that there is a specific subpopulation of people with MDD who have a dysfunctional cortisol stress hormone response system, resulting in abnormal C-reactive protein levels (Haapakoski et al. 2015). When tested specifically for treatment of depression, the use of medications with anti-inflammatory effects such as infliximab and nonsteroidal anti-inflammatories was found to have significant benefits, but only for this sub-group (Kohler et al. 2014; Raison et al. 2013). In addition, a recent systematic review of randomized control trials found anti-inflammatory agents improved depressive symptoms compared to placebo both as adjunctive and monotherapies in patients with MDD (Kohler-Forsberg et al. 2019). While this specific abnormality may only account for a minority of patients with MDD, it makes the point that there is scope to better individualize treatments for particular subpopulations. This increased stratification of patients could, therefore, lead to improved clinical response rates and, in turn, increased patient satisfaction. Increased pharmacological specificity comes with additional benefits for future drug manufacturing as well. As it stands, for a pharmaceutical product to make it to market requires it to have significant benefits and a low side-effect profile for a large proportion of a given patient population. With precision psychiatry, there could be an aim to design psychotropic medications that may not work for everyone, but which could have large benefits for smaller groups.

There is also a wealth of exciting research into how genetic variance can influence the effectiveness of the range of treatment regimens, particularly with MDD and anxiety disorders. Variations within the promoter
of serotonin transporter gene (SLC6A4), one of the key regulators of antidepressant mechanisms, have been repeatedly associated with differing treatment response to antidepressants (Stevenson 2018). Patients with specific polymorphisms in this key gene display higher rates of MDD, poorer therapeutic response to serotoninergic antidepressants and increased side effect profiles (Luddington et al. 2009). Another gene that has been implicated in MDD is MTHFR, which is involved in folate metabolism but has particular high-risk alleles that result in reduced folate production (Bjelland et al. 2003; Hiraoka et al. 2017). Studies have shown that the addition of 15mg/day of folate, as an adjunctive therapy in SSRI-resistant MDD, increases response rates and results in greater improvements in depression symptom scores when compared to SSRI + placebo, although patients were not specifically tested for the high-risk genotype or folate deficiency (Papakostas et al. 2012). These are just two of many examples, which show that by understanding these diseases at the level of genes and proteins, there are opportunities to identify potential targets for novel treatments and move beyond the one-size-fits-all, protocelled approaches in use today.

Utilizing new technologies

The other big change on the horizon that precision psychiatry is poised to take advantage of is the growth and integration of machine learning and big data. As technology, the internet, and social media continue to expand its influence in our lives, there is access to more data, cheaper storage, and increased computing power. In a society that is increasingly subject to the risk of our data being mishandled, it would be refreshing to see it used to improve clinical outcomes for patients with mental illness instead. Machine learning can be defined as the ‘field of study that gives computers the ability to learn without being explicitly programmed’ (Munoz 2014). It has a range of advantages over traditional research methods, including increases in the potential for high-quality studies. In addition, machine learning utilizes a more accurate method for model testing. It employs a prospective approach, using smaller ‘training datasets’ to design models then trying to validate them against ‘testing datasets’ to evaluate their accuracy and update based on what they find (Bzdok et al. 2018). By using this training and testing approach, it attempts to identify and reduce the various biases that often distort traditional models and make research findings more generalizable. Computer systems are also better suited to handling complex data that deals with multiple outcomes (Bzdok et al. 2018). While randomized controlled trials may determine superiority between two treatments, they tend to fail when dealing with complex interventions as the comparisons and analyses become far more difficult (Baron et al. 2013).

These methods are already finding their place within psychiatry. One study of consenting patients who presented to a large emergency department used a model to analyze the language in their Facebook posts and was able to identify depressed patients with accuracy similar to standard depression screening surveys (Eichstaedt et al. 2018). Using clinical and imaging data, machine learning algorithms have successfully been employed to predict 1 year functional outcomes for patients in clinical high-risk states for psychosis or recent-onset depression (Koutsouleris et al. 2018). They have also been used on large datasets from clinical trials regarding response to antidepressants in MDD. One such study applying this method looked at citalopram and was able to predict clinical remission in 65% according to self-reported Quick Inventory of Depressive Symptomatology (QIDS) scores, higher than the base rate of predicted efficacy for citalopram and the percentage of patients who should achieve remission for a given treatment (Chekroud et al. 2016). The model was trained using 25 variables including components of the QIDS and Hamilton Depression Rating Scale and socioeconomic factors such as employment status and years of education. By combining the use of machine learning algorithms with traditional experimental designs and statistical inference methodologies, there is much scope to improve research output and develop useful clinical tools.

Potential challenges

The integration of precision psychiatry is a unique opportunity but presents with equally unique challenges, some ethical, some technical, and some practical. It is a venture that needs extensive collaboration and sharing of knowledge, requiring an integrated approach from psychiatrists, data scientists, industry, academia, and government. This interdisciplinary approach can ensure that patients remain at the center of care. Some issues with machine learning surrounding transparency, privacy, and accountability are still unanswered. The models are often complex with some operating as ‘black boxes’, which can make analysis difficult. With the increase in this type of research, there are calls to create frameworks to ensure that both the methods and results are trustworthy. One such call outlines three issues, namely, explainability, transparency, and generalizability, which need to be addressed before trustworthiness can be established (Chandler et al. 2020). There is also the issue of applicability for researchers as these methods can be difficult to implement and interpret for non-specialists. To combat this, there is a move toward developing software that
reduce the requirement for advanced programming backgrounds (Dwyer et al. 2018). However, even with these interfaces, there will inevitably be further challenges adapting workforces and IT systems to meet these evolving requirements. If algorithms learn from the data they are trained upon then, they may develop similar issues to their human counterparts including but not limited to racial and gender biases (O’Neill 2016). Availability of the large, unbiased, and representative data sets that are required for these models is, therefore, an additional challenge. The cornerstone of psychiatric management is the biopsychosocial model. In a struggle for finite resources, we must be cautious that increased emphasis on the biological component does not distract from providing proper funding for proven interventions, both at the level of the individual and broader, public health-based initiatives. Indeed, some areas of precision psychiatry rely heavily on psychosocial inputs, for example, using electronic health records to predict suicide attempts and deaths with machine learning algorithms (Simon et al. 2018). Additionally, diagnosis is often complicated by the presence of overlapping and co-existing disorders. While precision psychiatry aims to determine whether there is justification for differentiating these genetically or pathophysiologically, efforts must be made to avoid research that forces ‘precision’ in situations where it has no clinical utility. Finally, this new approach will require an acknowledgement of its value from the psychiatric establishment and a willingness to adapt to new methods.

Conclusion

In summary, we have outlined evidence of the growing influence of precision psychiatry. We suggest that increased patient stratification and integration of genetic information can improve therapeutic response rates, allowing us to move away from one-size-fits-all, protocolling treatment approaches. We argue that machine learning algorithms are already being employed in research, to better predict and improve patient outcomes. We also acknowledge some of the potential challenges and pitfalls that may hinder the precision approach. There have been many advances in precision psychiatry thus far, and the scope for how it could change practice in mental health disciplines is vast. While there is still much to discover, we must strive to implement these new techniques, progressing from research to trials and eventually clinical practice, where it can start to benefit our patients.

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Ethical standards

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