Personalized psychiatry: many questions, fewer answers

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Clinical practice in many areas of medicine is shifting toward personalized treatment. In other words, clinicians aim to treat patients based on their individual characteristics, including clinical presentation and/or biological markers. Biomarkers can help clinicians select the most effective treatments or reduce the risk of side effects by avoiding certain treatments in susceptible patients. In addition, new treatments are being developed for specific patient populations based on better understanding of disease processes associated with identifiable markers.[1] Advantages of an individualized approach are obvious — patients should receive treatments that are effective and better tolerated. And in theory, personalization of treatment should lead to lower health care costs. Medical spending continues to increase in most countries (more or less in parallel with increases in life expectancy).[2] Personalization should optimize health care spending by selecting treatments that are effective and avoiding those that are unnecessary.

Psychiatry is following the same trends, but its situation is seemingly more difficult. Psychiatric disorders represent a mix of diagnostic categories of variable validity and predictive value. Practically all medications used to treat psychiatric disorders have been discovered in a nonsystematic, serendipitous way or have been derived from existing prototypical drugs. Most psychiatric conditions are probably heterogeneous, which makes the search for biomarkers even more imperative, as practically no treatments are universally effective in patients whose conditions are diagnosed within broad and nonspecific categories. At present, we do not have any clinically applicable biomarkers in a narrow sense (laboratory test), yet there exist clinical findings that might allow personalization of treatment in patients with certain psychiatric conditions. Clues to individualized treatments are hardly recognized in current treatment guidelines, which are often based on levels of evidence derived from clinical trials in undifferentiated patient samples. Arguably, in most areas of psychiatry, predictors of treatment response or side effects are simply unavailable. Studies have attempted to find such predictors; however, many of them were derived in studies designed for purposes other than response prediction and rely on variables that could be viewed as opportunistic. Nevertheless, there are examples of psychiatric treatments that can be selected rationally without resorting to a trial and error approach and that can make a great difference for patients, their families and society.

So where in psychiatry can we do better than chance? There are some promising examples, but they seem to be lost in the vast sea of DSM 5 diagnostic categories. Disorders that offer the most promise with respect to effective treatment selection might be periodic catatonia, bipolar disorder responsive to lithium and melancholic depression. These are also among conditions where treatment can make a substantial difference with respect to disability; on the other hand, benefits of treatments for cognitive (neurodegenerative) disorders or substance abuse are quite limited.[3] So it is those relatively few selected treatments indicated in specific patient populations that can produce excellent results (if applied properly), but that can also be overlooked easily, perhaps for one of the following reasons.

Low expectations and stigma

A factor that needs to be taken into account is the often low expectation that some clinicians may have with respect to outcomes of psychiatric disorders. Such expectations are not infrequently based on observations of patients who could do better, but are "well enough." I wonder to what extent this is also a consequence of medical and postgraduate training. Residents mostly see patients in emergency departments, inpatient units or chronic care settings, but rarely encounter patients who have fully recovered and have more or less resumed normal lives. In a similar fashion, many clinical trials commonly target an arbitrarily defined change on a rating scale, such as 50% improvement over a relatively short period of time, instead of full recovery. Such studies may have an heuristic value in uncovering some basic aspects of treatment response, but their usefulness in recommending a treatment that would be fully effective in the long term is low.

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The potential for individualized treatment exists in only a few areas

For many common psychiatric disorders, there are simply not enough data to allow for meaningful clinical predictions. For instance, one of the most important causes of morbidity and disability worldwide is major depression. Yet, it is conceptualized as a broad diagnostic category with low reliability and questionable validity; not surprisingly, treatment trials in depressed patients have produced relatively modest results. To illustrate this point, in the STAR*D study, a pragmatic trial of major depression in a broadly diagnosed cohort of patients, less than half showed response (defined as better than 50% reduction of severity of symptoms) to first-line treatment with citalopram, and less than one-third achieved remission.[4] Predictors of the outcome of depression have been studied repeatedly with inconsistent and mostly negative results, including multiple genetic markers from recent genome-wide association studies (GWAS).[5] Certain clinical features that were initially proposed have been perpetuated with little supporting evidence; an example is the notion of familiality of treatment response, which was initially proposed as a hypothesis based on a limited case series in the 1960s[6] and 1970s[7] and then perpetuated as a proven fact in psychiatry textbooks. To this day, only 1 systematic study has shown familiality of response in a single trial of fluvoxamine.[8] Another important concern about depression is that it is often recurrent, so acute trials may be less relevant for its long-term treatment and outcome. Proper testing of clinical predictors will be difficult, expensive and not always embraced by the pharmaceutical industry, which may anticipate a reduction in the target populations for any more selective drugs.

Lack of clinical precision

In the absence of diagnostic tests, psychiatry relies on a detailed clinical assessment with careful consideration of the clinical picture, long-term course, previous treatment history and family/genetic history. Such assessments take a considerable amount of time and effort, for instance, to obtain collateral information. As a result, patients are sometimes assessed incompletely. Remick and colleagues[9] reviewed the quality of family history documented in patients' charts and found that while presence of major psychiatric illness in a family was usually documented accurately, its type (subtype) was not. Yet, for accurate prediction it is exactly the specific and accurate detail that is needed!

Much of modern medicine deals with diseases that are multifactorial, that have some genetic basis and that are very likely heterogeneous (e.g., diabetes, hypertension, ischemic heart disease, arthritis, chronic obstructive pulmonary disease). In this respect, psychiatry is not that different. We have to be prepared for the fact that, from the pragmatic point of view, many medical and psychiatric conditions are heterogeneous and could be divided into numerous and much smaller subgroups, each with more or less specific treatment. For instance, in patients with non–small cell lung cancer, certain markers typically present in less than 10% of patients are associated with a response to specific treatments.[1] Another example is a new treatment for cystic fibrosis, VX-770, based on a particular mutation (G551D) found in about 4% of all patients with cystic fibrosis. That translates into roughly 1200 cases in the United States.[10] In comparison, bipolar disorder affects more than 3% of the general population and, of patients with this diagnosis, 30% might respond favourably to lithium.[11] Following the basic principles of predictive testing, it is obvious that biomarkers can be typically most useful when they are applied to populations with higher prevalence of the trait in question. Progress in genetic mapping with the arrival of GWAS and whole genome sequencing raised hopes of accelerated biomarker development. However, such studies, GWAS in particular, typically target small genetic effects in large and most likely heterogeneous populations, and thus their immediate outcomes may be less applicable than originally thought.

The cost of personalized medicine

An important aspect of personalized medicine is its economic dimension. While personalized medicine should lower the health care cost relative to its benefits, some of the new treatments can be very expensive. For instance, recent treatments derived from genetic findings can exceed $100 000 per year in addition to the cost of screening.[10] The development of new drugs in general is a costly and lengthy process, and this will be even more the case for treatments targeting smaller patient populations. The cost then needs to be put in perspective against the actual benefits that may range from a relatively minor extension of survival to practically complete remission. All this leads to more questions. Psychiatric disorders are common, often affect young people and are lifelong. Is society prepared to invest in psychiatry in the same way as in other areas of medicine? In patients with bipolar disorder or schizophrenia who achieve full remission, reduction of costly hospital admissions and recovery of social and occupational functioning represent a clear economic benefit. However, clinical improvement does not result only from better medications. Specialty programs have advantages with respect to multiple outcomes, including disability and mortality.[12] Another successful example is the relapse prevention program ITAREPS developed by Spaniel and colleagues[13] for patients with psychotic disorders. Close monitoring and tailoring the clinical management based on text messaging has demonstrated the potential to optimize antipsychotic treatment and avoid costly hospital admissions.[14] At the same time, in many areas of predictive testing we may end up not having treatment alternatives for patients who do not respond to certain treatments. For example, VX-770 is probably not going to be effective for those 96% of patients with cystic fibrosis who carry one of the 1800 known mutations different from G551D.[15] Similarly, in psychiatry, several studies have shown reasonable power of frontal θ cordance to predict remission in patients with depression,[16] yet we still need to treat all depressed patients, including those who are predicted not to respond.

Conclusion

Personalization of medicine (and psychiatry) is a logical step in the right direction. However, its widespread adoption will see an increased direct cost, at least initially. This leads to the inevitable question of whether society is willing to make such an investment in an area that is still fighting stigma. Particularly relevant for psychiatry is the notion that we need to study patients who got better as a result of treatment. This entails systematic and prospective follow-up and treatments according to research protocols in specialized settings. The possibility of relapse in patients with psychiatric disorders is lifelong, so it makes little sense to discharge patients from specialized programs once they get better. Exposure to such specialized programs also needs to be an integral part of medical and postgraduate training.

Last but not least, we should ask ourselves whether nonpersonalized medicine is at all possible. As clinicians, we make decisions every day based not only on diagnosis and symptoms, but also on our biases and previous experience. These decisions are often implicit rather than explicit, and attempt to make sense out of clinical complexities. It will be important to take the best of these observations and combine them with careful neurobiological and genetic research to improve outcomes of some of the most serious and costly diseases.

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