

Essay

An Introduction to Personalized Psychiatry

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"If the human brain were so simple that we could understand it, We would be so simple that we couldn't." -- Emerson Pugh

One of the earliest examples of genotypes causing a particular drug response phenotype, what we today call "personalized medicine," came about in the early 1990s, when studies began to show that Alzheimer's disease patients that carried the e4 allele of the apolipoprotein E gene were less likely to respond positively to treatment with cholinomimetic agents like physostigmine. This established a foundation for the field of individual pharmacogenomics. The promise of this field lay both in improved efficacy of treatment and the prevention of adverse drug reactions. In 1999 the British Medical Journal reported that 44000 to 98000 patients a year are killed by medical errors, with adverse drug reactions as a major cause of morbidity and mortality. From this expert panel, and other reports, such as the US Institute of Medicine's *To Err is Human* report later that year, the importance of preventing adverse drug reactions came to the forefront of the public consciousness. Could an individualized approach to pharmacological treatment be used to prevent a portion of these errors? The need for personalized medicine seemed clear, but nevertheless the translation of knowledge from the bench to the bedside has remained an obstacle.

This article provides an overview of the current state of personalized medicine in the field of psychiatry. Beginning with a case study about the history of clozapine, an early example of a drug redeemed by its value to particular individuals and patient populations, we go on to describe the historical challenges that personalized care has had to confront, both logistical and scientific, and then continue

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to discuss several major examples of recent successes in personalized psychiatry, and finally concluding with some thoughts about the future of the field.

Clozapine: A Case Study

Clozapine was Introduced in the 1960's by CIBA (now Novartis) and taken off the market because of cases of life-threatening drug induced agranulocytosis. It was reintroduced in the 1980's for treatment resistant schizophrenia patients and it was used more in this patient population because of the relative ease of monitoring for the appearance of agranulocytosis and other side effects. The reintroduction of clozapine started the atypical neuroleptics revolution. Clozapine induced agranulocytosis was once one of the most poorly understood adverse drug reactions in all of medicine, but research within the last decade has found that human leukocyte antigens are associated with clozapine-induced agranulocytosis risk in a robust and potentially clinically relevant fashion [1]. Clozapine is thought to be the most efficacious atypical antipsychotic agent in patients with treatment-resistant schizophrenia and has a proven threefold overall risk reduction for suicidal behaviors in schizophrenic patients [2]. The clinical difficulty is that this benefit must be weighed against the risk of clozapine-induced agranulocytosis, which occurs in approximately one percent of patients [3].

The mechanism of this side effect remains unknown and is a matter of considerable controversy. Immunological, genetic, toxic, or other complex multistep processes have been proposed for this life-threatening side effect [4]. Support for a genetic hypothesis is provided by findings indicating clozapine-induced agranulocytosis as an idiosyncratic drug reaction [5], by a 21-fold higher rate of this drug adverse reaction among Finnish people compared to other ethnic backgrounds [6], and by a case report of concordant manifestation of clozapine-induced agranulocytosis in monozygotic schizophrenic twins [7].

This straightforward picture, however, is complicated by replication difficulties. A major study by Jeffrey Lieberman and Edmund Yunis in the early 1990s [8] on specific HLA antigens associated with clozapine-induced agranulocytosis provoked much excitement in the field before their data failed to replicate in a major follow-up study [9]. A third study by Michael Dettling also failed to replicate the original Lieberman and Yunis results, and suggested a different set of HLA antigens as markers of clozapine-induced agranulocytosis risk [10]. A reasonable conclusion to draw here is that, although genetic background may play a crucial role in the induction of drug reactions such as clozapine-induced agranulocytosis we are far from being able to appreciate the patients' genotype-based risk. For this severe side effect, the complex nature of adverse drug reactions implies that interactions between many genes are likely to play a role.

The Historical Challenges

There is a disconnect between the statisticians, mathematicians, and computer scientists who invent techniques and the biologists and

clinicians who use them. For example, there have been numerous models for describing microarray data, but most of them are not used in practice. Biologists and clinicians are understandably reluctant to apply methods they do not themselves understand. Hence there is a trade-off between complexity and adoptability. The major breakthrough being sought is to find a group of treatments that can be tailored to a patient's specific genomic profile and illness subtype. Personalized psychiatry offers the promise of being able to depart from reductionism and provide better treatment efficacy with reduced dangers of toxic drug reactions and interactions.

The challenge for the future of personalized psychiatry is overcoming the limitations of the genetic studies themselves: failure to replicate, the cost of genotyping, the generalizability of American and European studies on Caucasian populations, and protecting patient's personal information. There is also the deeper issue of the validity of current genetic models. The statistician George Box once observed that "All models are wrong, but some are useful." The more we discover about the interactions of different genes the more weakness we discover in simplistic, linear models. In a nonlinear system doubling a stimulus (the input) does not necessarily double the response, and may even cause a qualitatively different response. A model represents only specific aspects of reality that are relevant to the question under consideration, and how detailed a model is does not make it right or wrong, but merely determines whether the model is appropriate to the problem to be solved. Measurements of the system output often do not suffice to choose between alternative models, as different system structures may still produce similar system behavior.

The Future is Now: Areas of Present Success

A 2004 study found that the major histocompatibility complex HLA-B*1502 is a strong predictor for Carbamazepine induced Steven - Johnson syndrome in Han Chinese individuals [11]. The odds ratio for developing carbamazepine induced Steven - Johnson syndrome in those positive for HLA-b*1502 were 2504, with Positive Predictive Value of 93.6% [11]. In response to this research the FDA issued a black box warning in 2007 for carbamazepine and recommended that patients of Asian descent be genotyped before being treated with carbamazepine, and similar associations are expected in the future.

Pathophysiology is advancing along with pharmacology: A 2013 research study "Toward a Neuroimaging Treatment Selection Biomarker for Major Depressive Disorder" found that relative hypometabolism in the insula of the brain predicted a poor response to pharmacotherapy and a strong response to cognitive-behavioral therapy, while insula hypermetabolism was associated with the opposite [12]. This heralds the promise of finding a neuroimaging "treatment-specific biomarker" that predicts differential outcomes to different therapeutic approaches. The results of this recent study have yet to be confirmed in prospective experiments.

In schizophrenia, the hippocampus is characterized by being both hypermetabolic and reduced in size, but it remains unknown whether these abnormalities are mechanistically linked, or what the pathophysiology of such a link might be. Another 2013 study addressed this question by using MRI tools that can map hippocampal metabolism and structure in patients and mouse models [13]. In at-risk patients, the researchers found that hypermetabolism begins in CA1 and spreads to the subiculum after psychosis onset. CA1 hypermetabolism at baseline predicted hippocampal atrophy, which

occurred during progression to psychosis. When acute exposure to ketamine produced a similar regional pattern of hypermetabolism, the repeated exposure shifted the hippocampus to a hypermetabolic basal state with concurrent atrophy and pathology in parvalbumin-expressing interneurons. Parallel in vivo experiments using the glutamate-reducing drug LY379268 and direct measurements of extracellular glutamate showed that glutamate drives both neuroimaging abnormalities. These findings show that hippocampal hypermetabolism leads to atrophy in psychotic disorder and suggests glutamate as a pathogenic driver.

A 2013 Israeli study on glutamatergic neurotransmission hypothesized that autoimmune effects on glutamine receptors and receptor subtypes (NMDA, AMPA, metabotropics, etc) could bring together into a biochemically-defined clinical syndrome conditions that are now vaguely defined based on clinical presentation [14]. For example, specific psychotic and mood dysfunctions now described as schizophrenia, schizoaffective disorder, or bipolar disorder type 1 could instead be considered different manifestations of anti-NMDA receptor encephalitis [14]. Disease states characterized by autoimmune-induced glutamatergic receptor dysfunctions rather than by phenomenology may be more amenable to personalized pharmacotherapy. Laboratory tests could allow treatment to be specific not only to pathological subtype but also to disease stage and progression, with early recognition and preventative care even among the only mildly symptomatic.

Better understanding the pathological basis of psychiatric disease states allows not only for novel treatment targets and rational drug design, but, more prosaically, for improved assessment of psychiatric disease that exists along a continuum. A clinical challenge throughout psychiatry is distinguishing between normal human unpleasant experience and pathological states. For example, consider the difference between the normal limits of human attention and concentration and the clinical syndrome of ADHD. Recent research has found evidence from quantitative genetic analysis of twin pairs that ADHD is not a distinct neurological malfunction but the extreme end of a continuous trait, with DSM-defined ADHD and subthreshold attention deficits having a strong genetic link [15]. It remains to be seen whether the etiology remains the same for different degrees of symptoms, or whether complex overlapping factors may be at work.

Future Expectations of Personalized Psychiatry

The end goal of personalized psychiatry would involve routine whole genome screenings in daily clinical practice using specific biomarkers and accepted treatment algorithms. Along the way to this destination personalized psychiatry promises the ability to treat early and even prodromal disease, and to allow for more combinations of medications with less interactions and risks of adverse side effects. The challenges to attaining these goals are many: diagnostic uncertainty and comorbidity muddy the research waters, mechanisms of action and psychiatric pathophysiology remain elusive, and the drug pipeline in psychiatry has been slowed in recent decades, with most drug treatments discovered by chance in the 1950s and 1960s, with little progress in novelty or efficacy since. The advancement of pharmacology in recent decades has mainly concerned tolerability. Problems with replication and effect sizes abound in the literature.

Dr. Evian Gordon, executive chairman of the Brain Resource Company, once noted that "Most Personalized Medicine research in

Psychiatry using molecular measures alone have failed to replicate. Whilst disappointing, this is not surprising, since 80% of human 25,000 genes have some effect on the brain.” Dr. Gordon also describes several other factors needed for personalized psychiatry to fulfill its promise: Neurobiological validation of specific constructs of psychiatric disorders, a neurodevelopmental focus in research, with an emphasis on the age of onset and peak periods when Psychiatry instabilities manifest, a dimensional context of psychiatric disorders, where underlying neurobiology is continuous from normality to disorder; large databases of norms for age and longitudinal clinical outcomes with clear end-points that can confirm or disconfirm biomarker treatment predictions, and a translational approach that links basic mechanism of psychopathology to targeted biomarkers that predict who is most likely to respond best to what intervention.

A new research approach, Research Domain Criteria, or RDoC, promises to address many of these challenges [16]. RDoC is a framework of five organizing domains that cut across traditional disorder classifications. The Research Domain Criteria (RDoC) are: Negative Valence Systems (Threat and Anxiety), Positive Valence Systems (Rewards and Habits), Cognitive Systems (attention, perception, working memory), Systems for Social Processes (identification of facial expression, Theory of Mind), and Arousal/Regulatory Systems (State and Trait dynamics). With RDoC, NIMH seeks to elucidate the underpinning biological mechanisms across the scale (from genes to circuits and behavior) of these five domains.

There is no debate that medications like the antipsychotics which were initially discovered by serendipity produced a major progress in the treatment of conditions like for example psychosis. Unfortunately through the years the research focused on the production of new psychiatric medications and did not break a lot of ground in answering the questions about the etiology of mental diseases [17]. On the current approach for treatment of Schizophrenia for example there are satisfactory clinical results in the acute stages of the disease due to the treatment with antipsychotic medications coupled with various forms of psychosocial treatments. However the relapse rate could reach up to 80% [18].

Nowadays the DSM diagnosis is still based on signs and symptoms and not on biomarkers or advanced neurocognitive testing identifying premonitory signs of the illness that will allow focusing on the preventive treatment [17]. I will end by quoting and excerpt from Dr. Thomas Insel article “Rethinking Schizophrenia” published in Nature in November 2010 [17]: “We need a personalized and preemptive approach, based on understanding and detecting individual risk and facilitated by safe and effective interventions”.

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