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Personalized medicine in major depressive disorder — Opportunities and pitfalls

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Abstract

The sequencing of the human genome in the early days of this millennium was greeted with great fanfare as this accomplishment was expected to revolutionize medicine and result in individualized treatments based on the genetic make-up of the patient. The ultimate promise of personalized medicine would be fulfilled with the identification of disease biomarkers that would be widely available for use in diagnosis and treatment. Progress, however, has been slow in providing disease biomarkers or approved diagnostic tests. This is true for major depressive disorder (MDD), despite its prevalence in the general population and the widespread acceptance of its biological basis. Studies using strategies like genome-wide association and candidate gene analyses have identified a number of possible biomarkers of MDD, including serum levels of neurotrophic factors, inflammatory cytokines and HPA axis hormones, but none have proven sufficiently powerful for clinical use. The lack of biologically based tests available for use in identifying patients with MDD is a significant impediment to personalized and more effective treatment, because it means diagnosis continues to be driven by subjective symptoms. While genetic studies of MDD have not yet led to diagnostic and treatment biomarkers, progress in determining the role of the genome in drug metabolism heralds the first effort in personalized prescribing for the antidepressants. The FDA suggested and approved genotyping tests for common variants of drug metabolism genes, such as the cytochrome p450s. By using these tests a physician can select an appropriate antidepressant for a given patient, as differences in clearance, half-life, and peak blood concentrations are controlled by genetic variability in drug metabolism. Personalization in drug choice can be achieved because these tests: (1) identify responders and non-responders; (2) provide alerts to possible adverse drug events; and (3) help optimize dose. Improved ways of diagnosing and prescribing effective treatments for MDD are needed, as the available methods are inadequate and symptom based. In the foreseeable future, further interrogation of the genome may serve as the basis for development of new personalized medicine strategies for diagnosis and treatment of MDD.

Keywords

Biomarkers; Genome; Genetics; Metabolism

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1. Introduction

"… the right pill at the right time for the right patient" is the promise of personalized medicine [1]. The sequencing of the human genome early in this millennium was lauded for the breadth of the scientific achievement and was expected to revolutionize medicine. Genomics would provide the links between our genes and biological events, whether normal or pathological. Armed with this blueprint, disease biomarker development would proceed rapidly and greatly improve clinical practice. Medical treatment would be individualized with targeted medicines based on the genetic and molecular profile of the patient. Here, we explore the challenges facing psychiatry with respect to a personalized medicine approach to major depressive disorder (MDD). Although often viewed as a single clinical condition, MDD is clinically heterogeneous with a high prevalence in primary care practice (~1 of every 10–20 patients). All ages and ethnicities are affected and currently diagnosis is dependent on the physician's interpretation of the patients' symptoms, because there is no biologically based diagnostic test for MDD. Our goal is to inform the "front-line" physician on the latest strategies for diagnosing and treating MDD from a personalized medicine perspective. We review how studies examining the contribution of genetics to development of MDD, the effectiveness of various antidepressant drugs, as well as the search for biomarkers, have fostered a more personalized medicine approach in MDD treatment. We discuss how pharmacogenetics may be contributing to a personalized medicine approach for the available MDD pharmacotherapies. Many individuals voice concerns to their primary care physician (PCP) long before they see a mental health professional [2,3].

2. The PCP and MDD in a Primary Care Patient Population

Due to its prominence (~20% in the general population) MDD often is referred to as the "common cold of psychiatry [2,4,5]. Worldwide, MDD causes significant economic ($83 billion in the US alone) and psychosocial burdens due to the cost of hospitalization, lost work productivity and suicide. MDD is a lifelong disorder; it may be chronic or characterized by frequent recurrences with a mean of about 6 episodes in 15years [6]. Up to 40% of sufferers remain untreated and suicide is a common consequence; about half of suicide victims visited a PCP within the month prior to their death [2,3,7]. With the advent of multiple SSRIs many more MDD patients now are being treated and maintained in primary care practices [4,8]. Learning how to recognize MDD, therefore, is a major obstacle facing the PCP.

Ideally, the PCP would have a sensitive and readily available blood test to aid in the diagnosis of MDD, but there are no accepted biomarkers or biologically based diagnostic tests. MDD symptoms further complicate diagnosis, because they can resemble normal emotions (e.g., sadness) that accompany many life events, but they are exaggerated and do not resolve when the cause ceases. Presentation often includes vague somatic symptoms (e.g., headache, fatigue) that may vary by gender and age, as well as racial heritage [2]. Thus, an Asian patient may complain of "tiredness" or "imbalance" while a Native American may be "heartbroken" [3]. Because of its prevalence the PCP should be alert to its presence in primary care settings. Many PCPs are reluctant to deal with mental illness, but

the topic should be discussed because the personal and societal burden of untreated depression is so costly.

3. Diagnosis & Treatment of MDD

Currently, the guidelines from the DSM-IV-R [9,10] are used to diagnose MDD. These guidelines include both inclusion and exclusion criteria as well as various qualifiers concerning the characteristics of the current episode and the course of the disorder. A major depressive episode is defined as a period of >2weeks where the patient experiences a depressed mood or the loss of interest or pleasure in nearly all activities (anhedonia), as well as difficulty in concentrating or sleeping, changes in appetite or weight, and thoughts of suicide or death. Symptoms lasting 2 or more years define chronic depression and cannot be due to alcohol, drugs, prescribed medication, a major medical condition or interspersed with periods of manic behavior. The constellation of symptoms also varies across patients. This hampers diagnosis and suggests that MDD is a heterogeneous disorder with possibly clinically distinct subpopulations or endophenotypes [11]. As no biologically based diagnostic tests are available, the subtypes of depression (e.g., seasonal affective disorder, postpartum, etc.) are based on the physician's interpretation of the patient's symptoms, observations of the patient, as well as the medical history of the patient and the patient's family. Specific guidelines are available to help the PCP recognize and manage MDD [12,13]. Screening instruments are available to use in diagnosis, but they remain subjective. Objective biomarkers, despite years of searching, are not yet available. The current diagnostic tools are symptom driven and include various questions asked when completing the patient history (e.g., "Have you been feeling down, depressed, or blue over the last 2weeks?") or are found in patient-completed questionnaires and scales (e.g., Beck Depression Inventory; Patient Health Questionnaire-9-item [PHQ-9]) [14–16]. The high prevalence of MDD suggests that such screening questions and instruments should be a necessary component of every patient history. Additionally, the NIMH provides brochures (e.g., NIH Publication No. TR 10-4779) about MDD written in lay language that can be placed in the PCPs' waiting and examination rooms. This provides the patient with easy access to information as well as opportunities for discussion between the patient and physician. Such materials are in the public domain and may be copied and reproduced without permission (nimhinfo@nih.gov).

Due to the lack of MDD biomarkers effective treatment is difficult at best and "trial and error" dominates much of the current clinical approach. Because the biological causes of MDD are still unknown, treatment tends to focus on symptom reduction rather than engendering remission of the disease. There are no diagnostic assessment tools that dictate the choice of one antidepressant over another and many placebo-controlled studies indicate that all the major classes can be effective [17]. This makes it difficult for the physician to predict which patients will display clinical improvement to a given drug [17,18]. Many patients stop taking their medication because of the significant amount of time, often 6–12weeks, required for remission or symptomatic improvement. Patients can achieve the same degree of clinical effectiveness whether it occurs early or late in treatment; early success does not indicate greater effectiveness of the prescribed drug. Many experience difficulty with side effects (e.g., weight gain, decrease in libido) and fully 42% of patients

stop medication within the first 30days of treatment. Often patients do not respond to a given antidepressant and abandon their follow-up visits to the PCP. This limits their opportunity for treatment with a different agent or the addition of a second drug; both strategies are used in non-responders and can be effective [19]. Being able to predict non-response early in treatment would help individualize drug selection but efforts directed towards this goal have yet to identify reliable predictors. Half of patients remain untreatable. Recent work, however, suggests that obtaining a combination of baseline features and early symptom changes post diagnosis, and initiation of medication, may have clinical benefit [20].

The focus on symptom reduction rather than remission makes it difficult for the PCP to tell the difference between the patient's usual mental state and one that may be pathological [7]. The ACNP Task Force report discusses MDD in the context of response, remission, recovery, relapse and recurrence [6]. Thus, despite seemingly insurmountable roadblocks, strategies are available to help the PCP to better individualize treatment and to quickly provide effective pharmacotherapy [1]. The PCP should make the patient aware of the frequently lengthy interval between the beginning of treatment and symptom relief and/or remission. Success in treating MDD requires frequent and truthful communication between the patient and the PCP as well as shared decision-making concerning treatment options.

4. Genomics and MDD — Biomarkers, Diagnosis and Individualized Treatment

The NIH defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention [21]. Establishing correlations between disease and changes in biomarkers would certainly lead to better patient care and lower medical costs, but this goal has been difficult to achieve. Often, the term biomarker is used in an imprecise fashion, as evidenced by the over 150,000 published papers claiming the discovery of various disease biomarkers, but with only approximately 100 biomarkers in clinical use. Many biomarker discovery efforts are based on investigator-initiated academic research with examination of fewer than 100 samples. This hampers efforts to develop clinically useful biomarkers because of a general lack of standardization of methods, a lack of statistical power and a lack of stringency in case definition prior to sample collection. Ultimately, this poses a problem for the large-scale validation studies needed to evaluate candidate biomarkers for all diseases, not just MDD.

The wide acceptance of a genetic contribution to MDD has prompted the use of candidate gene and genome wide association strategies to search for contributing genes. Identification of genes that will lead to biomarkers useful in diagnosis and treatment is a goal yet to be realized. Other strategies used in the search for clinically viable biomarkers have concentrated on the further characterization of MDD using brain electroencephalographic and imaging techniques, as well as the measurement of presumed blood indicators such as inflammatory cytokines, HPA axis hormones, metabolic markers and growth factors [22,23]. The association between these various biochemical domains and MDD has sparked interest in the development of a serum-based, multi-analyte biomarker panel utilizing a composite

score rather than the traditional single analyte approach. Such panels remain under development [11,24].

In biomarker candidate studies, genes are selected for evaluation based on existing knowledge and, in the case of MDD, the emphasis has been on what is currently known about MDD and the primary targets and putative mechanism(s) of action of antidepressants. A group of subjects is genotyped for a certain gene variant and then the effect of that variant on the disease of concern is calculated. As targeting is done *a priori*, the information gained in these studies is limited and this strategy usually does not identify new avenues of investigation. Rather, it confirms or negates the influence of the targeted genes; often the predicted strong associations are not borne out. A case in point is the failure to find the expected strong impact of genes involved in serotonin synthesis on antidepressant response [25]. Meta-analysis of "candidate gene" studies, such as the many examining the variants of the serotonin transporter gene and depression, has found little support for the supposed link. Such analyses support the idea that these "false positives" may be the result of singling out just one gene for study when a large number of them may contribute to the disease, suggesting that genome-wide association studies are more likely to succeed in identifying biomarkers of disease [26] but see [27].

Genome-wide association studies are considered "hypothesis-free" as they evaluate all known genes and their association with MDD and/or the response to treatment. Thus, this strategy is expected to identify novel and clinically relevant genes with the discovery of genetic variants associated with pharmacologic response. The genetic influence in MDD is considered to be through multiple genes. Take, for example, the case for involvement of serotonin; there are at least 30 to 40 genes controlling the amount of it in the brain. If only one gene of interest is examined, the likelihood of a false positive result is high [26].

Just as there are no accepted diagnostic biomarkers of MDD available to the PCP, there are none to direct the choice of a given antidepressant class or to predict the success of a given drug. Experimental studies in animals and peripheral leukocytes from MDD patients find that genes for trophic factors (BDNF, FGF, VEGF) controlling cell proliferation, growth, and resiliency, as well as pathways controlling cell signaling, neurotransmitter transport and metabolism, are impacted by antidepressant treatment [28]. Studies examining quantitative electroencephalographic responses, brain imaging and various serum analytes provide new avenues of investigation in MDD, but to date they have provided no clinical utility for selecting an antidepressant or determining its effectiveness during treatment. The many studies linking depression to a variety of possible structural and functional biomarkers as well as genomic, proteomic, and metabolomic measures are thought provoking. They also suggest putative biomarkers may not be stable or invariant over time but may change with the course of the disease and with treatment. This suggests that their measurement at baseline or early in treatment may increase their predictive validity, but the clinical utility of this strategy in a primary care setting remains to be seen [7]. Of course, the cost–benefit of the development and use of a biomarker must be considered and factored into the treatment costs for MDD. For example, neuroimaging biomarkers would not be cost-effective.

5. What the PCP Must Consider in Selecting an Antidepressant for MDD

Once MDD is diagnosed and the PCP decides to treat with an antidepressant, a number of hurdles must be faced in selecting the most suitable agent for a given patient. A high rate of therapeutic failure is the norm in MDD and, unfortunately, personalized medicine has yet to provide specific guidance for the PCP in terms of treatment selection. Finding an effective pharmacotherapy for a given patient is by "trial and error". No clear evidence base exists to aid in choosing among existing medications to *maximize* benefit for the individual patient.

The pharmacological classes used to treat MDD include the tricyclics, the selective serotonin reuptake inhibitors (SSRI)s, and the serotonin norepinephrine reuptake inhibitors (SNRI)s, monoamine oxidase inhibitors (MAOs) and more recently developed classes that largely target melatonin and nicotine receptors [29,30]. All of these classes of antidepressants have been found to be effective. The trial and error process in drug selection, however, often means the first drug prescribed is not effective. Various drugs of the same or different class will need to be tried until symptom reduction or remission is achieved. The PCP should determine patient preference, past treatment history, family treatment history, clinical symptoms, the expected side effect profile and safety, as well as the possible need for medical/laboratory monitoring. One certainty the PCP faces in drug selection is that antidepressants have significant toxicity in some patients. As discussed below, unlike diagnosis and prediction of antidepressant effectiveness, genetic information and testing allow for some individualization of treatment with respect to avoiding toxicity.

6. Pharmacogenomics — The Genetics of Variable Drug Response & Treatment of MDD

MDD patients receiving identical antidepressant treatment do not have identical responses; this variation encompasses drug therapeutic efficacy as well as drug metabolism, pharmacokinetics and toxicity. Pharmacogenetics, the understanding of how an individual's genetics affect the response to drugs, holds great promise for improving the outcome of MDD treatment by tailoring drug choice to a given patient's genetic makeup [31–33]. While progress is being made, many pharmacogenomic efforts aimed at finding genes predictive of therapeutic response have not yet come to fruition. Despite a number of positive leads no robust genetic predictors of the therapeutic response to antidepressants have been found [25].

However, there is one area where pharmacogenetics has made a contribution in the personalization of antidepressant selection and that is in identifying the genes contributing to drug metabolism. This genetic variation between individuals contributes to differential blood levels of certain antidepressants resulting in considerable patient differences in drug exposure, clinical response and toxicity. Many commonly prescribed antidepressants are metabolized by the cytochrome P450 (CYP) liver enzyme system, specifically CYP2D6, CYP2C19, CYP3A4, and CYP2C9 [1]. Genetic variants of these enzymes result in large individual differences in clearance, half-life, and peak blood concentration that ultimately influence individual drug response and toxicity. For example, the number of functional CYP2D6 alleles will result in a fast metabolizer (2 alleles) or poor (0 alleles) phenotype

[34,35]. Genetic tests are available to determine the variants in individual patients and the US FDA recommends their use to better individualize treatment for many classes of drugs, including the antidepressants. Labels for many of the antidepressants now contain such information. It would be of maximum benefit to the patient if the PCP could consider comparative data on the relative efficacy, tolerability, safety and acceptability of all the various antidepressants to aid in drug choice. While this information often is lacking, it is likely that such comparative data will be available in the future owing in no small measure to advances in pharmacogenetic profiling [30].

7. Contribution of Pharmacogenetics & Metabolism to Therapeutic Efficacy of Antidepressants and Individualized Treatment

Drug regulatory bodies such the US FDA recommend that patients be genotyped for specific genetic biomarkers before a physician prescribes certain common medications, including many of the antidepressants. Despite the wide availability of tests for genotyping patients for genetic biomarkers related to drug actions, physicians have been reluctant to adopt such screening. To date there is little integration of pharmacogenetics into clinical practice. Despite this fact, efforts continue in obtaining and providing this type of information to the PCP. In part this is accomplished by frequent additions and updates to drug labels based on new pharmacogenomics information affecting safety or efficacy in certain patient populations [36]. To aid the PCP in using the current drug metabolism knowledge in choosing an antidepressant for an individual patient, there is valuable information regarding the pharmaco-metabonomic phenotyping issues in the Table of Pharmacogenomic Biomarkers in Drug Labels available at the FDA site (http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378). Additional valuable information is found at the Personalized Medicine Coalition site (http://www.dddmag.com/Personalized-Medicine-Advances-But-Faces-Challenges111611) and in the guidelines made available by Clinical Pharmacogenetics Implementation Consortium (http://www.pharmgkb.org). Physician education in the use of such genetic information and individualization of treatment are the goal of such sites. The fact that such information is readily available may herald the beginnings of success for personalized medicine in MDD. The PCP should be aware there are opposing views as to the real contribution of pharmacogenomics and genotyping to personalized medicine in clinical practice, as well as the cost-effectiveness of testing for these variants in dose adjustment. Many, including health-insurance companies and health care providers, still need to be persuaded that personalization in drug selection provides enough benefits to justify the cost. Further genotyping may have more clinical importance in diseases like MDD, where there are high rates of non-responders, as all methods providing information on individual drug response can be of clinical significance [34,37,38].

8. Summary

The PCP should be aware that MDD is relatively common in the general clinical practice patient population and it is costly in terms of lost function as well as mortality. Because there are no biomarkers for MDD, and no biologically based diagnostic tests in clinical use, the PCP must screen for this disorder on the basis of symptoms verbalized by the patients or

when gathering the initial or updated patient history. The PCP also should be aware that the symptoms of MDD vary by gender, age and ethnicity. The lack of biomarkers or diagnostic tests makes it is difficult for the PCP to predict antidepressant efficacy and to make appropriate drug selection. The PCP must advise patients that finding an effective treatment may require a considerable amount of time. This effort is time well used, as it will help decrease the number of patients who stop treatment. Currently, personalized medicine will not help the PCP in predicting which antidepressant will be effective for a given patient. However, existing information on genetic biomarkers and the availability of genotyping tests concerning genetic control of drug metabolism and associated toxicity will aid the PCP in selection of a safe antidepressant for that patient, and in minimizing factors that may influence patient compliance. A truly personalized medicine approach for MDD only will be achieved when identification of biomarkers of MDD results in the development of widely available and cost-effective diagnostic tests. Research directed toward the discovery of biomarkers of depression and treatment resistance is of the utmost importance in this endeavor.

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