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Physicians' opinions following pharmacogenetic testing for psychotropic medication

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ABSTRACT

Pharmacogenetics seeks to improve patient drug response and decrease side effects by personalizing prescriptions using genetic information. Since 2012, by one estimate, the number of patients who have had pharmacogenetic testing has doubled and this number is expected to double again by 2015. Given the increasing evidence for genetic influences on treatment response, we deemed it important to study physicians' opinions of pharmacogenetic testing. Surveys were completed by 168 Canadian physicians who had ordered at least one pharmacogenetic test (in particular for CYP2D6 or CYP2C19) for the prescription of psychiatric medication. Our results indicated that 80% of respondents believe genetic testing would become common standard in psychiatric drug treatment and 76% of respondents reported satisfactory or higher than satisfactory understanding of the pharmacogenetic report provided. Significantly more male physicians believed they had a higher understanding of the pharmacogenetic report compared to female physicians. To our knowledge, this is the only study that has assessed physicians' opinions of pharmacogenetic testing for psychotropic medication after they had received a pharmacogenetic report. Our results demonstrate a positive opinion of physicians on pharmacogenetics and indicate great potential for future clinical application.

1. Introduction

The current 'trial and error' method of prescribing medication is insufficient in clinical practice, as selection of drugs is often based on external factors such as nationality, age and gender of the prescribing physician (Kirchheiner et al., 2004). With this system, there is a great deal of uncertainty with whether the patient will experience therapeutic effects of the medication or, alternatively, an adverse reaction. Pharmacogenetic testing aims to genetically guide prescriptions to improve patient response and decrease side effects. In Canada, 7.5% of patients admitted to hospitals experience one or more adverse drug reaction, 36.9% of which are deemed highly preventable. These adverse reactions carry a financial burden for the healthcare system, resulting in longer stays for patients, and accounting for an estimated 9250–23,750 preventable deaths annually in Canada (Baker et al., 2004). Pharmacogenetics is a branch of personalized medicine which utilizes genetics and pharmacology to predict individual drug response, ultimately leading to safer and more effective treatments for patients.

1.1. Genetic basis for treatment response and side effects

Although a variety of environmental and lifestyle factors affect

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individual drug response, genetic factors have a major effect (Gibbs et al., 2005). One group of such factors is the genes encoding for CYP450 liver enzymes. CYP450 enzymes are a group of mixed function monooxygenases that are responsible for metabolizing almost 50% of all marketed drugs (Gibbs et al., 2005). CYP450 enzymes play a key role in catalyzing detoxification reactions and have been the target of many pharmacogenetic studies.

Polymorphisms in the CYP450 genes yield enzymes with different pharmacodynamic and pharmacokinetic properties. After DNA analysis of the specific polymorphisms in CYP450 genes, predictions of how an individual will metabolize a certain drug can be made. An individual may be classified as an extensive metabolizer (EM), intermediate metabolizer (IM), poor metabolizer (PM), ultra-rapid metabolizer (UM) (Gibbs et al., 2005). Given this information, physicians' are better able to predict how well a drug will be metabolized and can select a specific medication and dose that will maximize efficacy and minimize the likelihood of a potentially fatal adverse event (Sallee et al., 2000). Although in practice, most patients being tested will have an EM status, this information is also useful for the clinician to identify outliers who are non-EM status and who carry higher risks for non-response or side effects.

1.2. Clinical utility

Despite the apparent benefit of pharmacogenetics, it is not yet part of common practice. A nationwide survey of 10,303 US physicians published in 2012 found that only 12.95% of physicians had ordered a pharmacogenetic test in the previous 6 months (Stanek et al., 2012). One of the largest barriers preventing the ubiquitous use of pharmacogenetic testing is the lack of evidence to support its clinical utility. While Singh et al. (2014) generally indicated that pharmacogenetic testing is valuable, their review article concluded that the current evidence is not yet persuasive enough to support routine pharmacogenetic testing. However, the authors also stated that in the future, comparing genetically guided vs. unguided trials will be helpful to determine its clinical utility (Singh et al., 2014). Conversely, the Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines demonstrated that CYP2D6 and CYP2C19 polymorphisms have a major effect on the efficacy and safety of tricyclics (Hicks et al., 2013). Furthermore, a one year blinded and retrospective study found that individuals taking a psychiatric drug for which they are a poor metabolizer or ultra-rapid metabolizer (CYP2D6, CYP2C19, CYP2C9, CYP1A2, serotonin transporter gene (SLC6A4), or serotonin 2A receptor gene (5HTR2A) were examined) had 69% more total health care visits, 67% more general medical visits, over three times as many medical absence days, and more than four times as many disability claims in comparison to individuals taking drugs for which they are extensive metabolizers (Winner et al., 2013). In addition, the FDA currently includes information regarding safe consumption and metabolic statuses in their product labeling for many psychotropic drugs (Drozda et al., 2014). The accumulating literature to support the clinical utility of pharmacogenetics has sparked major growth. In the largest commercial testing effort to date, there have been over 100,000 pharmacogenetic tests used for the prescription of psychotropic medication across North America (DeDiemar, 2014).

1.3. Current opinions

Although the field of pharmacogenetics is steadily growing, there are many other barriers preventing the integration of pharmacogenetic testing into a major healthcare system: cost of tests, time to receive results, laboratory resources, physicians' current knowledge to facilitate and interpret results, and physicians' attitudes toward pharmacogenetic testing. Regardless of all other barriers, if physicians are not willing to order pharmacogenetic tests, they will never become part of common practice. Thus, it is clear that physicians' perception of pharmacogenetic testing will play a large role in whether or not these genetic tests will be used.

Attitudes toward pharmacogenetic testing may be influenced by a variety of factors such as age, sex, religion, level education, personal experience, and much more. In general, previous studies assessing psychiatrists' views of psychiatric genetics have shown that most believe that several psychiatric disorders have 'moderate' to 'high' genetic contribution (Klitzman et al., 2014). A recently published paper surveyed 910 undergraduate and medical students in southern Ontario assessing their views on pharmacogenetic testing (Lanktree et al., 2014). Interestingly, despite fears that genetic test results may be used for other purposes without consent (71%) or may lead to genetic discrimination (78%), the vast majority (90%) of students were in favor of pharmacogenetic testing (Lanktree et al., 2014). Other papers have examined the opinions of qualified healthcare professions such as pharmacists and various physicians. A study in Québec, Canada, found that 95.6% of pharmacists would recommend pharmacogenetic testing to guide prescription once they have been trained (de Denus et al., 2013). Another paper examined primary care physician's views and concluded that physicians were highly interested in ordering pharmacogenetic tests but only 13% indicated that they felt comfortable doing so (Haga et al., 2012). This was largely due to lack of knowledge; 25% of participants stated they had no education regarding pharmacogenetic testing (Haga et al., 2012). A study published in 2008 assessed psychiatrists' attitudes towards pharmacogenetic testing and found that 82% of psychiatrists felt pharmacogenetic tests would be somewhat useful or extremely useful to predict the risk of an adverse reaction (Hoop et al., 2008).

To date, many of the studies that have examined healthcare professionals' views of pharmacogenetic testing have focused on their interest in ordering the tests and their perceived ability to interpret the results if they had received a report. To the best of our knowledge, there have been no studies that have assessed physicians' opinions of pharmacogenetic testing along following their experience of having ordered and used a pharmacogenetic test. The aim of this study was to assess physicians' perception of pharmacogenetic testing and their experience using the test results to help prescribe antidepressant and antipsychotic medication.

1.4. The Pharmacogenetic Research Clinic at the Centre for Addiction and Mental Health (CAMH)

The Pharmacogenetic Research Clinic at the Centre for Addiction and Mental Health, Toronto, Canada, has been established in 2008 and is co-directed by Daniel J. Müller and James L. Kennedy. The main goals were (1) to test feasibility of delivering genetic information to physicians and patients, (2) evaluate clinical utility by assessing patients prospectively over three months before and after their physicians have received a genetic report, and (3) to evaluate acceptance by physicians and patients by means of a survey analysis (Pharmacogenetics in Psychiatry Follow-up Questionnaire; PIP-FQ). Initially, the CYP2D6 and CYP2C19 gene were selected as first step and an interpretation of the metabolizer status was sent to the physicians (Müller et al., 2013). This study is named Genetics of Drug Metabolism and Response (DMR) and results of the feedback questionnaire will be presented. The DMR study was subsequently enlarged where additional CYP enzymes were added (CYP2C19, CYP1A2, and CYP3A4), more healthcare service centers were included to refer patients, and more rapid genotyping was delivered (within 48 h after inclusion). This study started in 2011 and is named The Individualized Medicine: