Pharmacogenomics of antidepressants for major depressive disorder

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ABSTRACT

Major depressive disorder (MDD) is a common disorder, affecting approximately 10% of adults in the United States each year. The primary treatment options for moderate to severe MDD are antidepressant medications, mainly selective serotonin reuptake inhibitors (SSRIs). Current guidelines recommend an initial trial of 4-8 weeks to determine if a medication is effective for a patient. Through the use of pharmacogenomics, it may be possible to predict whether patients will respond to and tolerate SSRIs. This article discusses several genes and alleles that may play a role in a patient's response to SSRIs.

KEYWORDS

major depressive disorder, pharmacogenomics, antidepressants

Major Depressive Disorder (MDD) is a common, under-treated disorder that affects approximately 10% of adults in the United States annually.[1] Major depressive disorder can be debilitating for many people and the goals of treatment are to induce remission of these symptoms and return the individual's level of functioning. The main treatment options for moderate to severe MDD are antidepressant medications, mainly selective serotonin reuptake inhibitors (SSRIs).[2] However, response to these medications is slow and current treatment guidelines recommend an initial therapeutic trial of 4-8 weeks to determine a patient's response to the medication.[2] Yet, even with extensive clinical experience with these medications, a high percentage of patients continue to have poor response or intolerable side effects.[3] By using pharmacogenomics, it may be possible to screen and predict whether patients will respond to antidepressants and be able to tolerate the medications.[4]

Pharmacogenomics of antidepressants involve both pharmacodynamic (PD) and pharmacokinetic (PK) properties of these medications. The efficacy of SSRIs can be explained by PD effects and their activity at neurotransmitters. The adverse effects of SSRIs are more correlated with the PK or metabolism of these medications. Thus far, there have been several genes and alleles that have been identified that may play a role in the response to SSRIs.[4, 5] For example, the genetic variants of the SLC6A4 serotonin transporter gene have been extensively studied with regards to SSRI response, specifically at the 5-HTTLPR-promoter region.[4, 5] Based on the presence of either a base-pair insertion or deletion in this region, there exists two alleles—the long ***(l)*** or short ***(s)*** allele. The long ***(l)*** allele has been associated with twice the expression of the serotonin transporter, thus creating more targets for these medications that may improve SSRI outcomes.[4] This allele is present in about 50-60% of Caucasians and about 30-40% of Asians.[4] A meta-analysis of 15 studies demonstrated that the ***ll*** genotype was associated with higher remission rates and four week response rates whereas the ***ss*** genotype was associated with lower rates of remission with SSRI therapy.[6] A more recent meta-analysis found an association between the ***l*** allele and treatment response and remission in Caucasians; however, this relationship may not be relevant in Asians.[7] Furthermore, the serotonin 1A and 2A receptors (HTR1A and HTR2A) have been implicated in improving response to SSRIs and were extensively studied in the STAR*D trial that included 1953 subjects with MDD who were treated with citalopram for 14 weeks.[8] The HTR2A ***rs7997012*** A allele was associated with a higher likelihood of response to SSRI than patients homozygous for the G allele.[8] The catechol-o-methyltransferase gene (COMT) gene has also been studied for its role in individual variation in SSRI response in patients with MDD.[4] COMT is a key enzyme that causes methylation of catecholamines and thus variation in its activity could affect the efficacy of the SSRIs. The researchers in one study identified 23 SNPs in the COMT gene from DNA collected in the previously mentioned STAR*D trial.[9] They identified one specific SNP, ***rs13306278***, that had a significant association with

remission in Caucasian, non-Hispanic subjects.[9] Furthermore, another study examined the role of COMT variants in duloxetine response in MDD as measured by their 17-item Hamilton Rating Scale for Depression (HAM-D-17).[10] They found that three variants, ***rs65737, rs165588, and rs165737,*** were associated with changes in HAM-D-17 scores.[10] These studies demonstrate that there may be several genes/alleles yet to be identified that play an essential role in SSRI response. Serretti et al investigated a novel single nucleotide polymorphisms (SNP) in the PTGS2 gene on antidepressant response and remission in a small sample of patients with MDD.[11] PTGS2 gene encodes an enzyme necessary for the synthesis of prostaglandins, and there is a theory that they may play a role in the pathogenesis of MDD.[11] However, based on the results of this study, there did not appear to be any evidence that these SNPs in the PTGS2 gene are associated with changes in antidepressant response.[11]

As mentioned above, genetics can play a key role in how patients respond to antidepressants, but they have an equally important role in detecting potential adverse effects in patients, which can lead to treatment discontinuation. Common side effects of SSRIs include gastrointestinal side effects (nausea, vomiting, diarrhea), central nervous system side effects (insomnia, anxiety, headache) and sexual side effects including decreased libido and impaired ejaculation.[12] Most of the antidepressants, including SSRIs, are metabolized by the P450 enzyme system including CYP2C19 and CYP2D6.[13] These enzymes have many polymorphisms, which can affect the degree of drug metabolism and the degree of side effects.[14] There are over 78 different variants of the CYP2D6 enzyme that predispose individuals to being either ultra-rapid metabolizers (UMs), extensive metabolizers (EMs), intermediate metabolizers (IMs), and poor metabolizers (PMs).[5, 14] In one study, patients identified as poor metabolizers who received medications influenced by CYP2D6 isoenzyme had significantly more moderate or marked side effects compared to individuals identified as rapid or ultra-rapid metabolizers.[15] Furthermore, another study demonstrated that the 5-HTTLPR ***s*** allele was associated with higher rate of adverse effects and treatment discontinuation among patients taking paroxetine.[16] It appears that pharmacogenetics may play a role in identifying potential adverse effects in patients to prevent medication non-adherence.

While the scientific evidence for the potential role of pharmacogenomics in predicting response and adverse effects in MDD are abundant, guidelines for clinical utility of pharmacogenetic testing for antidepressants are limited. The prescribing information for SSRIs generally does not include specific considerations or recommendations for pharmacogenetic testing. For example, the prescribing information for citalopram recommends that "20 mg/day is the maximum recommended dose for CYP2C19 poor metabolizers" although there is no guidance as to who may be tested for CYP2C19 metabolism.[17] In 2007, The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group, developed by the National Office of Public Health Genomics at the Centers for Disease Control and Prevention (CDC), evaluated the evidence for pharmacogenetic testing for SSRIs. Upon completion of the evidence review, they "found insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for non-psychotic depression."[18] They also stated that more studies were needed that analyzed drugs individually and not necessarily as a class for SSRIs.[18] There is a pharmacogenetic test available on the market, the AmpliChip that tests for polymorphisms in the CYP2C19 and CYP2D6 enzymes.[19] It was developed by Roche Diagnostics as the first FDA-approved genetic test for these polymorphisms.[4,19] This test could potentially give clinicians useful information when making decisions about antidepressant treatment selections.

In conclusion, pharmacogenomics may play a critical role in determining patient's response and tolerability to antidepressant medications. The utility of pharmacogenetic testing in clinical practice remains unclear and currently, there is no formal recommendation to conduct testing prior to initiating antidepressant treatment. Additional studies are needed to determine the clinical and economic benefit of pharmacogenetic testing prior to or during antidepressant treatment for patients with depressive disorders.

REFERENCES

1. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):617-27. DOI: 10.1001/archpsyc.62.6.617. PubMed PMID: 15939839.
2. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder, Third Edition [online]. November 2010. Available at http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx. [Accessed on August 7, 2011]
3. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006;163(1):28-40. DOI: 10.1176/appi.ajp.163.1.28. PubMed PMID: 16390886.

4. Kirchheiner J, Seeringer A, Viviani R. Pharmacogenetics in psychiatry - a useful clinical tool or wishful thinking for the future?. Curr Pharm Des. 2010;16(2):136- 144. DOI: 10.2174/138161210790112728.
5. Psychiatry. In: Pharmacogenomics: Applications to Patient Care. Second edition. ed. Lenexa: American College of Clinical Pharmacy; 2009.
6. Serretti A, Kato M, De Ronchi D, Kinoshita T. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. Mol Psychiatry. 2007;12(3):247-57. DOI: 10.1038/sj.mp.4001926. PubMed PMID: 17146470.
7. Porcelli S, Fabbri C, Serretti A. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. Eur Neuropsychopharmacol. 2012;22(4):239-58. DOI: 10.1016/j.euroneuro.2011.10.003. PubMed PMID: 22137564.
8. McMahon FJ, Buervenich S, Charney D, Lipsky R, Rush AJ, Wilson AF, et al. Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. Am J Hum Genet. 2006;78(5):804-14. DOI: 10.1086/503820. PubMed PMID: 16642436.
9. Ji Y, Biernacka J, Snyder K, Drews M, Pelleymounter LL, Colby C, et al. Catechol O-methyltransferase pharmacogenomics and selective serotonin reuptake inhibitor response. Pharmacogenomics J. 2012;12(1):78-85. DOI: 10.1038/tpj.2010.69. PubMed PMID: 20877297; PubMed Central PMCID: PMC3113454.
10. Houston JP, Kohler J, Ostbye KM, Heinloth A, Perlis RH. Association of catechol-O-methyltransferase variants with duloxetine response in major depressive disorder. Psychiatry Res. 2011;189(3):475-7. DOI: 10.1016/j.psychres.2011.07.002. PubMed PMID: 21788083.
11. Serretti A, Chiesa A, Calati R, Massat I, Linotte S, Kasper S, et al. No influence of PTGS2 polymorphisms on response and remission to antidepressants in major depression. Psychiatry Res. 2011;188(1):166-9. DOI: 10.1016/j.psychres.2010.11.023. PubMed PMID: 21168919.
12. Finley PR. Selective serotonin reuptake inhibitors: pharmacologic profiles and potential therapeutic distinctions. Ann Pharmacother. 1994;28(12):1359-69. PubMed PMID: 7696728.
13. Ereshefsky L, Riesenman C, Lam YW. Serotonin selective reuptake inhibitor drug interactions and the cytochrome P450 system. J Clin Psychiatry. 1996;57 Suppl 8:17-24; discussion 25. PubMed PMID: 8698676.
14. Lee KC, Ma JD, Kuo GM. Pharmacogenomics: bridging the gap between science and practice. J Am Pharm Assoc (2003). 2010; 50(1):e1-14; quiz e15-7.
15. Laika B, Leucht S, Heres S, Steimer W. Intermediate metabolizer: increased side effects in psychoactive drug therapy. The key to cost-effectiveness of pretreatment CYP2D6 screening?. Pharmacogenomics J. 2009;9(6):395-403. DOI: 10.1038/tpj.2009.23. PubMed PMID: 19451914.
16. Murphy GM Jr, Hollander SB, Rodrigues HE, Kremer C, Schatzberg AF. Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression. Arch Gen Psychiatry. 2004;61(11):1163-9. DOI: 10.1001/archpsyc.61.11.1163. PubMed PMID: 15520364.
17. Forest Pharmaceuticals, Inc. Celexa(r) (citalopram) prescribing information. St. Louis, MO. January 2009.
18. Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. Genet Med. 2007;9(12):819-25. DOI: 10.1097GIM.0b013e31815bf9a3. PubMed PMID: 18091431.
19. de Leon J, Susce MT, Murray-Carmichael E. The AmpliChip CYP450 genotyping test: Integrating a new clinical tool. Mol Diagn Ther. 2006;10(3):135-51. PubMed PMID: 16771600.

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