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Antidepressant Dosing in Major Depression: A Pharmacogenomic Approach

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Antidepressant Dosing in Major Depression: A Pharmacogenomic Approach

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Abstract

Major depressive disorder (MDD) is the most predominant mental disorder in the United States, with serious and costly health risks if not successfully managed. Pharmacotherapy is a standard option for MDD treatment, but patients often require extensive therapy adjustments to find a suitable regimen. Pharmacogenomics may enable greater precision in antidepressant therapy. Genotypic variations in CYP2D6 and CYP2C19 metabolic enzymes are reliable predictors of serum drug concentration, but the complex dose-response relationship of antidepressants prevents such variations from predicting therapy success. Additionally, ABCB1 has been examined for its role in P-glycoprotein efflux of antidepressants in the brain, yet it is still inconclusive as to which variations are correlated with drug response. Current genotypic guidelines are largely proactive and clinical trials utilizing genotypic dosing have shown significant reductions in side effects and health care costs. Further studies of genotypic targets are needed and, if the possible clinical benefits are confirmed, the use of genotyping will be an important tool in optimizing antidepressant therapy.

Key Terms

ABCB1 Protein, Human; Antidepressants; Tricyclic; Cytochrome P450 CYP2C19; Cytochrome P450 CYP2D6; Depression; Depressive Disorder, Major; Genotype; Health care Costs; Mental Health; p-glycoprotein; Pharmacogenetics; Psychotherapy; Serotonin Uptake Inhibitors

Depression Background

The National Institute of Mental Health (NIMH) defines major depressive disorder (MDD) as "severe symptoms that interfere with your ability to work, sleep, study, eat and enjoy life. An episode may occur only once in a person's lifetime, but more often a person has several episodes."[1] Depression can be caused by a multitude of factors, a few of which include environmental, genetic, psychological and biological influences. Patients with MDD typically experience a low quality of life.[2] Often, depressed patients experience a decrease in physical, social and role functioning more than individuals with other chronic conditions such as diabetes or osteoarthritis. Patients with MDD often report poor intimate relationships, poor social interactions and social irritability. These individuals typically have a greater household or financial strain as well. It is also common for depression patients to experience limitations in the workplace, exhibit poor overall health and have a higher level of missed days of work.

Major depressive disorder is the most prevalent mental health disorder in the United States.[3] It is estimated that 6.7 percent of adults in the United States experienced a major depressive episode in 2014. The female population was more likely to experience these episodes (8.2 percent) versus the male population (4.8 percent). Major depressive episodes were also more prevalent in adults aged 18 to 25 years (9.3 percent) compared to adults aged 26 to 49 years (7.2 percent) and those aged 50 years and older (5.2 percent). The prevalence of MDD was even greater in adolescents aged 12 to 17 years (11.4 percent) than in adults in 2014. In this adolescent age group, the female population was also more likely to experience a major depressive episode (17.3 percent) than males (5.7 percent). Prevalence in adolescents increased with age. Twelve-year-olds had a prevalence of 5.7 percent while 17-year-olds had a prevalence of 15.1 percent.

While MDD varies between patients, the NIMH identifies several signs and symptoms that may indicate the onset of depression.[1] A few of these include feelings of hopelessness, pessimism, guilt, worthlessness, fatigue, decreased energy, insomnia and persistent sad, anxious or empty feelings. A depressed patient may also experience thoughts of suicide, have difficulty concentrating, making decisions and remembering details.

The diagnosis criteria for MDD has been described by the American Psychiatric Association (APA) in the fifth edition of the Diagnostic and Statistic Manual of Mental Disorders (DSM-5).[4] The diagnosis criteria are summarized in Table 1. It is important to note that an individual responding to a significant loss, such as financial or loss of a loved one, may exhibit some of the criteria specified in section A of Table 1; therefore, the medical professional's clinical judgment must be exercised to determine if this constitutes a major depressive episode.

Upon diagnosis of MDD, the APA recommends psychiatric management which includes establishing and maintaining a therapeutic alliance.[5] The patient should undergo a psychiatric assessment and be evaluated for safety, functional impairment and quality of life. The patient's care should be coordinated with other clinicians, and his or her psychiatric status should be monitored. The health care team should integrate measurements into psychiatric management, assist with treatment adherence and provide education to the patient and the family.

The acute phase of MDD treatment begins with the initiation of treatment.[5] This often constitutes the introduction of pharmacotherapy but may also include depression-focused psychotherapy, a combination of the two, electroconvulsive

Table 1. Diagnostic Criteria of Major Depressive Disorder (MDD).[4]

A. The patient must demonstrate at least five of the following symptoms, which must have been present almost every day during a consecutive 14-day period. It is important to point out that these symptoms must demonstrate a change from the patient's normal functioning. These symptoms may be given as a subjective report or as observed by others. Several of the diagnosis criteria may present differently in children as noted below.	
The patient must demonstrate at least one of the following.	• Depressed mood for the majority of the day. (Note: In children and adolescents, may present as irritable mood.)
	• Noticeably decreased interest or pleasure in all, or nearly all, activities for the majority of the day.
The patient must demonstrate at least four of the following.	• Notable weight loss when not attempting to diet or weight gain or change in appetite. (Note: In children, may present as failure to make expected weight gain.)
	• Insomnia or hypersomnia.
	• Psychomotor agitation or retardation (this criterion must be noted by others and not solely based on subjective feelings of the patient of uneasiness or being slowed down).
	• Fatigue or lack of energy.
	• Feelings of inadequacy or excessive or inappropriate guilt (which may be deranged), not solely self-blame or guilty feelings about being sick.
	• Decreased ability to think, concentrate or make decisions.
	• Frequent thoughts of death that expand beyond fear of dying, periodic suicidal thoughts without a definitive plan, a suicide attempt or a definitive plan for committing suicide.
B. The symptoms must cause a significant distress or impairment in normal daily functions such as social, occupational or other important areas of operation.	
C. The symptoms exhibited must not be attributed to any other factor such as the psychological effects of a substance or a symptom of another medical condition.	
D. The major depressive episode as expressed above must not be better attributed to a psychotic disorder, including schizophrenic disorders.	
E. The patient must not have experienced a manic or hypomanic episode. The exception to this criterion is if the episode can be attributed to another medical condition.	

Adapted from: American Psychiatric Association: Desk Reference to the Diagnostic Criteria from DSM-5. Arlington (VA): American Psychiatric Association; 2013. Major Depressive Disorder; p. 94-95.

therapy (ECT), transcranial magnetic stimulation (TMS) or light therapy. For patients with mild to moderate MDD, the APA recommends an antidepressant as initial treatment. In individuals with severe MDD, the APA deems an antidepressant necessary for treatment unless the patient plans to undergo ECT. The medications initially recommended for depression patients include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), mirtazapine, or bupropion. The individual agent, however, may be chosen based on anticipated side effects, patient's ability to tolerate the drug, safety considerations targeted to the individual patient and pharmacologic properties of the drug itself. These properties include the half-life, drug-drug interactions and the drug's action on cytochrome P (CYP) 450 enzymes. Monoamine oxidase inhibitors (MAOIs) are typically reserved for patients who do not respond to first-line treatments.

Careful monitoring should occur during the acute phase, and dosage or drug modifications should be made based on side effects or adverse events.[5] When assessing the efficacy of an agent in a particular patient, the medication should be discontinued after one month if the patient shows no signs of symptomatic improvement. If a patient is unresponsive or only partially responsive after four to eight weeks, the drug and dose should be adjusted and reevaluated in another four to eight weeks. When adjustments are necessary, the dose is titrated first as long as the patient has not experienced any adverse events and the side effects are well-tolerated. If a dose adjustment does not demonstrate any improvement, the patient may be prescribed a different medication either from the same class or another class of antidepressants. A patient is considered to be in the acute phase of treatment until he or she has demonstrated a response to medication. A response may not appear with the first treatment choice, so the acute phase is not limited to a specific time frame and may continue for an extended period of time.

Once a patient has demonstrated some success with an agent in the acute phase, he or she moves on to the continuation phase.[5] Here, the patient is monitored for potential relapse while on the medication initiated with success in the acute phase. This drug is typically continued for four to nine months, and the APA recommends depression-focused psychotherapy for prevention of relapse. A patient may move onto the maintenance phase of therapy using the same agent he or she used in the acute and continuation phases with success, but the medication may be adjusted to a full therapeutic dose. The maintenance phase is strongly recommended for patients who have high risk factors for recurrence of a major depressive episode. These risk factors may include family history of depression or mood disorders, presence of psychosocial triggers or appearance of lingering symptoms. Maintenance treatment continues indefinitely unless a patient and physician come to the decision to discontinue treatment. If pharmacologic treatment is discontinued, the dose should be tapered to prevent relapse and discontinuation symptoms. The patient should also be counseled on the signs of a relapse and have a plan in place if such an incident occurs. Monitoring of the patient should continue for several months after discontinuation.

While there are many options for initiating antidepressant therapy, adverse effects and poor efficacy often lead to a game of trial and error. This can waste money and time on an ineffective agent. It often takes at least one month to determine if the chosen treatment will be successful in a particular patient, so it may take months to years for a patient to find the right medication in the acute treatment phase to control his or her MDD. Genomic testing can help determine how a patient will react pharmacokinetically and pharmacodynamically to a particular drug and increase the likelihood of choosing an effective drug therapy at the initiation of treatment.

CYP2D6 and CYP2C19 PK/PG

The *CYP2D6 and CYP2C19* genes code for members of the CYP450 liver enzymes, which are heavily involved in the metabolism of many antidepressant medications.[6,7] CYP2D6 metabolism influences clearance of the SSRIs fluvoxamine and paroxetine and, also, tricyclic antidepressants (TCAs) such as amitriptyline, clomipramine, desipramine, imipramine, nortriptyline and trimipramine. CYP2C19 metabolism is observed with SSRIs including citalopram, escitalopram and sertraline, as well as TCAs like amitriptyline, clomipramine, imipramine and trimipramine.

Both *CYP2D6 and CYP2C19* have numerous polymorphisms in the population, with some alleles coding for decreased or increased activity compared to the standard function seen in the most common genotypes.[6,7] Combinations of these alleles result in several phenotypic classes: poor, intermediate, extensive and ultrarapid metabolizers. Two of the primary concerns are that poor metabolizers build up higher plasma concentrations of antidepressants and may be at greater risk of toxicities and side effects, while ultrarapid metabolizers may be more likely to experience treatment failure if plasma concentrations are too low. Pharmacogenomic guidelines have been developed and published for many SSRIs and TCAs to adjust dosage or recommend alternative therapies. However, the clinical significance for these guidelines is still being debated and is additionally complicated by an uncertain dose -response relationship of antidepressant medications.

A pair of studies by Hodgson and colleagues with information from the Genome-Based Therapeutic Drugs for Depression Project (GENDEP) questioned the association of pharmacogenomic dosing and SSRI/TCA side effects and treatment response.[8,9] The first study examined 223 patients on escitalopram and 161 patients on nortriptyline using a pragmatic design and flexible dosing protocol, where serum antidepressant concentration was assessed 8 weeks after treatment.[8] Patients were additionally genotyped. Variation in *CYP2C19* significantly correlated with escitalopram concentration ($p=9.35*10^{-9}$), while *CYP2D6* genotype was significantly associated with nortriptyline levels ($p=1.90*10^{-6}$). Neither genotyping nor serum concentration was significantly related to treatment response for either medication. The

second study examined the connection between CYP450 genotype and side effects with escitalopram and nortriptyline.[9] No significant association was found between genotype and side effects; serum concentration significantly predicted only a few minor effects, including the risk of dry mouth ($p= 0.0107$), diarrhea ($p=4.96*10^{-4}$) and dizziness ($p=3.28*10^{-5}$) with escitalopram, and dry mouth ($p=0.0331$) with nortriptyline. The authors acknowledged possible bias from the pragmatic design and flexible dosing, recognizing limited application of the results and the need for further study. This study demonstrates, again, that CYP genotyping is ineffective for predicting patient response.

ABCB1 PK/PG

The *ABCB1* gene codes for the amino acid transporter P-glycoprotein (P-gp) in many organs, including brain capillary endothelial cells where it drives out substrates and helps maintain the blood-brain barrier (BBB).[10] Many drug classes, including the TCAs, SSRIs and SNRI venlafaxine are substrates for P-gp and have limited uptake into the brain because of this efflux activity. Because of this limitation, genetic variation in *ABCB1* could result in altered P-gp function and clinically significant changes in antidepressant distribution to the brain.

A 2015 meta-analysis by Breitenstein and colleagues examined 16 pharmacogenetic studies associating *ABCB1* variants and antidepressant outcomes for MDD patients ($n = 2,695$).[10] A total of six single nucleotide polymorphisms (SNPs) were separately analyzed based on all studies, inpatient samples, outpatient samples, Caucasian only samples and without co-medication sub-groups. The SNP rs2032583 was associated with treatment outcomes across all studies ($p = 0.035$) and among all inpatient subjects ($p = 1.5*10^{-5}$), while SNP rs2235015 was associated with treatment outcomes only among all inpatient subjects ($p = 3.0*10^{-4}$). Both of those SNPs were intronic, meaning they did not alter the protein structure of P-gp but may modify brain delivery of antidepressants through unknown mechanisms. It was noted that the majority of the studies included did not have fixed dosages but were adjusted based on patient condition. If drug doses were decreased because of side effects, P-gp activity and BBB penetration may have been reduced and remain undetected.

Schatzberg and colleagues genotyped 10 *ABCB1* SNPs in 683 MDD patients, including all six SNPs analyzed in the Breitenstein meta-analysis.[11] Patients were randomized to treatment with escitalopram, sertraline or venlafaxine ER for at least two weeks (576 subjects completed eight weeks of therapy), with treatment efficacy assessed by the 16-item Quick Inventory of Depressive Symptomatology- Self Rated (QIDS-SR). Only SNP rs10245483 was significantly associated with prediction of remission (Wald statistic $W=12.64$, $p<0.001$, odds ratio $OR=3.48$). Common allele (G) homozygotes had significantly better response to escitalopram ($p=0.032$) and sertraline ($p=0.020$) than minor (T) allele homozygotes, which had significantly better response to venlafaxine ($p=0.018$); heterozygote genotypes had no significant differences across treatment. Similarly, major allele carriers had less adverse effects with escitalopram ($p=0.037$) while venlafaxine was associated with fewer side effects in minor allele homozygotes ($p=0.017$). The T minor allele has been reported to cause higher P-gp expression and may cause increased SSRI clearance, causing the observed, decreased efficacy. Venlafaxine activity as an SNRI may explain why it was more effective with minor alleles. The researchers acknowledged limitations in that serum drug concentrations were not collected and how as a pragmatic study the dosages were slightly lower than traditionally used in clinical drug trials, which could have altered response.

Clinical Applications

While pharmacogenomic data continue to be collected, many challenges remain in identifying factors significant to treatment outcomes. In addition to the studies specifically examining the genes coding for CYP enzymes or P-gp transporters, several genome-wide association studies have attempted to detect genetic variations connected with antidepressant outcome in MDD. The three largest were the GENDEP project, the Munich Antidepressant Response Signature (MARS) project and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.[12] A meta-analysis of data by the investigators of the three studies, including 2,256 subjects of Northern European descent with MDD, tested 1.2 million SNPs for association with symptom reduction and remission for up to 12 weeks of antidepressant therapy. No individual variant met significance criteria in the main analysis, suggesting antidepressant success to be likely due to numerous minor genetic effects instead of one primary pathway. However, the analysis was limited by the absence of placebo groups in any of the three studies as well as by the heterogeneity of the trials, and the authors concluded that larger cohorts of systemically treated and observed subjects were needed to conclusively test the approach.

Despite the inability to precisely identify the genetic regions associated with antidepressant response, there is some evidence suggesting genotypic-dosing may be a cost-effective tool in antidepressant treatment dosing. A one-year retrospective study of antidepressant therapy was conducted by Winner and colleagues in 2013, where 96 depressive or anxiety disorder subjects were tested for *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP1A2*, *SLC6A4* and *5HTR2A* genotypes.[12] Subjects had their medication and genotype combinations categorized as "red-bin," "yellow-bin" or "green-bin" based on the degree of caution and monitoring required as developed by the AssureRx Health GeneSight, a genotype interpretive report.[13] Nine subjects were categorized as red bin, with 48 yellow and 39 green. Compared to the green or yellow bin, subjects with a medication in the red bin had 69 percent more total health care visits during the year ($p= 0.014$). Also, nonpsychiatric medical visits were 67 percent higher for the red bin ($p= 0.039$). While red bin assignment was associated with greater numbers of psychiatric medications, there was no correlation between the number of drugs taken and any of the dependent measures, suggesting increase in health care utilization was directly related to red bin status. The authors concluded that pharmacogenomic information can better

define treatments and increase therapeutic response as well as decrease costs.

A 2015 study by Singh and colleagues provided buccal swabs for DNA analysis to 148 subjects with MDD, but only half were randomized to genotypic testing for *CYP2D6, CYP2C19* and *ABCB1* polymorphisms with dosing guided by the results.[14] Remission rates were assessed by the Hamilton Depression Rating Scale (HDRS) every four weeks for 12 weeks, with rating blinded to treatment groups. Remission from MDD was 2.52 times more likely with the guided treatment (95 percent confidence interval (CI): 1.71-3.73, p<0.0001), while the unguided group was 1.13 times more likely to experience treatment intolerability issues (95 percent CI: 1.01-1.25; p=0.0272). The guided group also had significantly lower risk of requiring sick leave (4 percent versus 15 percent, p=0.0272) and shorter length of leave (4.3 days versus 7.7 days, p=0.014). However, the trial results were not stratified by medication prescribed or genetic profile, so extrapolation of findings to specific drugs or polymorphisms is not possible.

Genotypic Guidelines

There are currently no dosing guidelines for *ABCB1* genotypes, but the Clinical Pharmacogenetics Implementation Consortium (CPIC) has published guidelines for SSRIs and TCAs based on *CYP2D6 and CYP2C19* genotypes.[7,8] Their recommendations are compiled in Table 2 and Table 3.

Conclusion

Major depressive disorder is one of the most common mental illnesses in the United States. A large range of therapeutic options, significant adverse effects and a complex dose-response relationship contribute to the uncertainty in optimizing antidepressant therapy. Pharmacogenomics has attempted to explain some of the variability observed, but

Table 2. CYP2D6 Phenotypic Guidelines for Antidepressant Drugs.[6,7]

Drug	Poor Metabolizers	Intermediate Metabolizers	Extensive Metabolizers	Ultra-rapid Metabolizers
TCAs: Amitriptyline, Nortriptyline, Clomipramine, Desipramine, Imipramine, Trimipramine	*4/*4, *4/*5, *5/*5, *4/*6 Avoid due to potential for side effects, consider alternatives not metabolized by CYP2D6. If used, consider 50% reduction of recommended starting dose (S).	*4/*10, *5/*41 Consider 25% reduction of recommended starting dose (M).	*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *10/*10 Initiate therapy with recommended starting dose (S).	*1/*1xN, *1/*2xN Avoid due to potential lack of efficacy, consider alternatives not metabolized by CYP2D6. If used, consider increasing starting dose (S).
Fluvoxamine	*3/*4,*4/*4, *5/*5, *5/*6 Consider a 25-50% reduction of recommended starting dose or use an alternative drug not metabolized by CYP2D6 (O).	*4/*10,*4/*41, *5/*9 Initiate therapy with recommended starting dose (M).	*1/*1, *1/*2, *1/*4, *1/*5, *1/*9, *1/*41, *2/*2,*41/*41 Initiate therapy with recommended starting dose (S).	*1/*1xN, *1/*2xN, *2/*2xN No recommendation due to lack of evidence (O).
Paroxetine	*3/*4,*4/*4, *5/*5, *5/*6 Select alternative drug not metabolized by CYP2D6, or consider a 50% reduction of recommended starting dose (O).	*4/*10,*4/*41, *5/*9 Initiate therapy with recommended starting dose (M).	*1/*1, *1/*2, *1/*4, *1/*5, *1/*9, *1/*41, *2/*2,*41/*41 Initiate therapy with recommended starting dose (S).	*1/*1xN, *1/*2xN, *2/*2xN Select alternative drug not metabolized by CYP2D6 (S).

Recommendation strength: S-strong, M-moderate, W-weak, O-optional

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Table 3. CYP2C19 Phenotypic Guidelines for Antidepressant Drugs.[6,7]

Drug	Poor Metabolizers	Intermediate Metabolizers	Extensive Metabolizers	Ultra-rapid Metabolizers
SSRIs: Citalopram, Escitalopram, Sertraline	*2/*2, *2/*3, *3/*3 Consider a 50% reduction of starting dose or select alternative drug not metabolized by CYP2C19 (M).	*1/*2, *1/*3, *2/*17 Initiate therapy with recommended starting dose (S).	*1/*1 Initiate therapy with recommended starting dose (S).	*17/*17, *1/*17 Initiate therapy with recommended starting dose, consider alternative drug not metabolized by CYP2C19 (M).
TCAs: Amitriptyline, Clomipramine, Imipramine, Trimipramine	*2/*2, *2/*3, *3/*3 Consider a 50% reduction of recommended starting dose or select alternative drug not metabolized by CYP2C19 (O).	*1/*2, *1/*3, *2/*17 Initiate therapy with recommended starting dose (S).	*1/*1 Initiate therapy with recommended starting dose (S).	*17/*17, *1/*17 Initiate therapy with recommended starting dose, consider alternative drug not metabolized by CYP2C19 (O).

Recommendation strength: S-strong, M-moderate, W-weak, O-optional

current data are unable to provide specific mechanisms. The metabolic enzyme activity of CYP2D6 and CYP2C19 has been shown to be connected to the plasma concentration of many antidepressants, but the clinical response to antidepressants does not necessarily have a linear relationship to drug concentration; guidelines for *CYP2D6* and *CYP2C19*-based dosing are largely proactive and unconfirmed. While *ABCB1* has been examined for its involvement in drug delivery to the brain, there is inconclusive evidence on which variations are significantly associated with antidepressant response. Further studies are needed to identify significant genetic pathways. While early trials already indicated possible efficacy of genotype-guided drug therapy, further analyses will be required to confirm its benefit. Given the high long-term cost of treating depression, and further health care costs if treatment fails, even modest improvements in patient response could justify the use of genotyping.

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