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Outcomes in Treatment of Major Depressive Disorder: Pharmacogenomic Testing vs. Treatment as Usual

Zachary Horoshak
University of North Dakota, zachary.horoshak@und.edu

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By

Zachary Horoshak

Bachelor of Science-Respiratory Care, Concordia University St. Paul

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Contributing Author Julie Solberg PA-C

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Abstract

The goal of this systematic literature review is to evaluate the efficacy and cost effectiveness of pharmacogenomic testing (PGx) versus treatment as usual (TAU) in the treatment of major depressive disorder (MDD). According to Huang & Lin (2015), MDD is characterized by multiple signs and symptoms consisting of mood, vegetative, cognitive, and even psychotic behaviors that may cause substantial impairment in the functioning and quality of life in an affected individual. This literature review consisted of articles found in PubMed, Cochrane, and PsychINFO which were extensively reviewed. Articles prior to 2008 were excluded due to the ever-changing landscape of PGx testing. In this review, 18 articles and studies were analyzed. This review found favorable outcomes when treatment was guided by PGx versus TAU while examining response and remission rates. Although data varied, cost effectiveness suggested some positive results with PGx although further investigations are needed due to limitations and lack of studies. Despite many favorable outcomes, more evidence of the effectiveness of PGx is needed to make a concrete recommendation that PGx guided treatment is superior to TAU. Information in this review will help clinicians decide if this is an appropriate option for the treatment of MDD. With continued research and ongoing studies this biotechnology is becoming more available to the mainstream.

Keywords: depression, major depressive disorder, pharmacogenomics, pharmacogenetics, treatment as usual, pharmacotherapy, medication, selective serotonin reuptake inhibitors, antidepressant, psychiatry and Patient Health Questionnaire (PHQ-9)

Does the use of Pharmacogenomic Testing Improve Depression Outcomes Better Than Treatment as Usual?

Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013), "major depressive disorder (MDD) is characterized as a serious illness that causes a person to feel deeply sad (or wholly absent of feeling) most of the day, nearly every day, for at least two weeks". According to Greenberg, Fournier, Sisitsky, Pike, & Kessler (2015), depression is one of the most burdensome illnesses worldwide and contributes to many unfavorable side-affects leading to functional impairment and disability. Depression is the leading cause of disability in the United states with an average of 400 million disability days each year. According to Greenberg at al. (2015), this is a much higher number than other mental and physical conditions.

Pharmacogenomics is the study of how genes affect an individual's response to medications. Pharmacogenomic testing can be utilized to see what medications may be the most effective for a patient with the least amount of side effects. Though the utilization of PGx appears beneficial in choosing a medication tailored to a patient's specific genes, the clinician should continue to keep age, lifestyle, side effects, cost, and comorbid factors in mind while using pharmacogenomics. MDD continues to be a significant health condition that impacts people regardless or devoid of age, race, or gender. Comorbidities are often associated with depression which can make appropriate management difficult. The goal of the clinician is to treat these patients with the best possible medication choice while mindful of side effects, cost, and outcomes.

This review will focus on medication management rather than other treatment modalities. Treatment as usual (TAU) with medication management is usually based on practice guidelines

and the clinicians own experience with certain medications that they believe will help control current symptoms. The purpose of this article is to evaluate whether PGx demonstrates improved clinical outcomes compared to TAU.

Statement of the Problem

Treatment of depression remains a difficult issue in primary care as well as psychiatric medicine. Many of these patients require multiple medication trials prior to finding a drug that works to control their symptoms without causing unfavorable side effects. This process may cause prolonged suffering with depression as well as a decrease in quality of life and productivity. The cost and time strain of attempting multiple medications continues to be a burden on the patient as well as the medical community.

Studies on pharmacogenomic testing for MDD are needed to demonstrate which medications may have higher efficacy and lower cost for both the patient and health care community. Medications are uniquely metabolized based on multiple genetic variants which pharmacogenomic testing can help identify. One consideration to remember while reviewing this paper is that many medications are not able to be analyzed with metabolism and genetic variances at this time, therefore only medications included in the pharmacogenomic testing databases are explored.

Research Questions

In patients with MDD, are medications guided by pharmacogenomic testing in the treatment of MDD more effective in achieving response and remission of symptoms compared with TAU based on depression assessment scales?

In patients with MDD, does medication management guided by pharmacogenomic testing improve cost effectiveness in the management of disease compared to TAU?

Research Methods

To prepare for this scholarly project multiple databases were searched using electronic databases which included PubMed, Cochrane, and PsycINFO to help find a wide array of topics relating to the treatment of MDD. The primary focus of the search was depression, pharmacogenetic/pharmacogenomic testing, and treatment in adults. In the research I utilized the following phrases, keywords, and MeSH terms: depression, major depressive disorder, pharmacogenomics, pharmacogenetics, treatment as usual, pharmacotherapy, medication, selective serotonin reuptake inhibitors, antidepressant, psychiatry and Patient Health Questionnaire (PHQ-9). The databases were further searched to narrow the topic down to major depressive disorder. Due to limitations in the number of studies found in the search, articles published from 2008 to the present were utilized. Several studies were excluded as they did not focus solely on MDD and contained a broader analysis of depression treatment in general. Articles utilized in this project contained meta-analyses, systematic reviews, randomized controlled trials, and cohort studies.

In this project the population of patients reviewed had a diagnosis of MDD. The studies evaluated were also specific to the adult population which included patients 18 years of age or older. Exclusion criteria included other mental conditions that may contribute or exacerbate the symptoms associated with MDD.

There are many different variables that need to be considered when treating MDD such as cost, side effects, comorbid conditions, and compliance. With the ever-growing amount of medications to treat this disorder along with the growing technology associated with PGx, it is an exciting time to work in a field that is so rapidly changing. Educating clinicians on these changes in healthcare will remain a top priority in the treatment of this debilitating disease.

Literature Review

A review of the literature has shown many positive outcomes associated with the use of PGx testing. Although there are limitations in each study, moving forward with pharmacogenomic testing should illuminate possible treatments that may have not been considered if the patient was receiving TAU.

Pathophysiology of Major Depressive Disorder

The Diagnostic and Statistical Manual of Mental Disorder (5th ed.; DSM-5; American Psychiatric Association, 2013) is widely used by clinicians and researchers alike to classify specific mental disorders. According to the DSM-V, Major Depressive Disorder (MDD) is diagnosed by having five out of the following nine symptoms. Depressed mood most of the day which occurs nearly every day, diminished interest or pleasure in almost all activities, significant weight loss categorized as 5% of body weight in a month, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive inappropriate guilt, diminished ability to think or concentrate, or recurrent thoughts of death/suicide or suicide attempt. Five of these nine symptoms must be present nearly every day, during a two-week time frame. These symptoms need to cause significant stress with social and occupational impairment. Also, these episodes may not be attributable to the physiologic effects of a substance or another medical condition (American Psychiatric Association, 2013).

According to Rot, Mathew, & Charney (2009), one in five Americans will experience an episode of MDD at least once in their life although most suffer more than one episode. In the past, most studies have focused on the monoamine neurotransmitters of dopamine and norepinephrine. This article discusses the multitude of possible attributing factors to the development of MDD which includes genetics, events from childhood, stress, structural and

functional abnormalities of the brain, abnormal function of the hypothalamic-pituitary axis, and interactions between genes and the environment a person is exposed to. The authors conclude that future research should focus more on individualized medicine with an emphasis on medication metabolism and independent genetic markers that may predispose a person to this condition.

In the meta-analysis by Verdujin et. al (2015), the involvement of different pathophysiological mechanisms such as inflammation, hypothalamic-pituitary axis, neurotrophic factors, and vitamin D are examined to see if their dysregulation is contributory to the diagnosis of MDD as well as the progression of MDD. This meta-analysis selected participants from the Netherlands Study of Depression and Anxiety (NESDA). The study focused on 2,831 subjects 18 to 65 years old who were either healthy controls or diagnosed with varying stages of MDD. The people in these studies were allocated from multiple different clinical practices such as psychiatry and family practice. The results suggested that mechanisms involved in the etiology of depression are not associated with the clinical progression of MDD. Strengths of this analysis were the large population of well diagnosed patients with variable socioeconomic status. Results showed a trend of increased CRP ($p=0.090$), increased cortisol ($p=0.025$), and decrease in Vitamin D ($p<0.001$) with the diagnosis of MDD, but the extent of change in these values were not associated with the severity and chronicity of the disease. No trend was seen between brain derived neurotrophic-factor (BDNF) and MDD in this meta-analysis. Results also showed that women who were active smokers with a lower education compiled with chronic diseases used selective serotonin reuptake inhibitors (SSRI's) and anti-inflammatory medication more frequently (Verdujin, 2015). Limitations were such that complications and other comorbidities were not discussed or evaluated in this article. It was also noted that samples retrieved were

either from a blood draw or saliva sample which comes from the periphery. This may not accurately demonstrate what process is taking place in the central nervous system (CNS) and may not represent these values properly, although most studies have examined peripheral DNA. Lastly, there are multiple models to stage MDD and may not be congruent with other studies that have utilized different staging models.

In the next article by Villanueva (2013) the goal was to evaluate studies that focus on the neurogenesis (growth and development of the nervous system) in those with MDD. The information in this article was collected over a span of twenty years with the purpose to hopefully help find new therapies and diagnostic tools to manage MDD. Different gene and protein expression that may affect the pathophysiology of MDD were examined. The evidence in this article supports the theory that disturbed neurogenesis is a factor in MDD. Although many circumstances such as traumatic events, chronic disease, neurological/endocrine issues, and substance abuse can contribute to the development of MDD, genetic factors have been linked to the diagnosis. Some of the genetic issues associated with MDD discussed in this article were low serum levels of brain-derived neurotrophic factor, micro RNA which helps regulate the control of genes, stress hormones of the HPA axis, inflammation, and gut microbiota (Villanueva, 2013). Controversial issues in this review include whether neurogenesis is the basis of the disease or if it is a response that may be induced by antidepressant treatments.

In an article by Fabbri and Serretti (2015), the complex nature of specific genes and pathways that may affect the approach to treatment of MDD can be partially evaluated by pharmacogenomics. The article discusses correlations between genes such as SLC6A4, HTR2A, BDNF, GNB3, FKBP5, ABCB1, and the cytochrome P450 system. The authors evaluated previous studies that have shown promising outcomes when pharmacogenomic testing is used to

detect different genes and pathways that may affect the medications mechanism of action. It is noted that gene studies have an advantage over TAU as PGx is focused on a biology supported hypothesis. With continued research it is hypothesized that pharmacogenomic testing will become mainstream in the treatment of MDD. Limitations include the vast number of genes not evaluated that may play a role in this disease.

Pharmacogenomic testing to aid in the treatment of MDD

In the meta-analysis performed by Rosenblat, Lee, and McIntyre (2018), the authors focused on two open-labeled and four blinded random controlled trials (RCT's). The quality of the studies in the meta-analysis were assessed using the Cochrane Handbook for Systematic Review of Interventions. All the studies included were funded at least partially by companies that were manufacturers of different pharmacogenomic tests to direct treatment. Response and remission rates were taken into consideration although one of the studies did not report response and another did not report remission. They reported response rates on 799 adult patients and remission rates on 735 adult patients. The Hamilton Rating Scale for Depression (HAMD-17) was used to assess the response and remission rates as well as safety and tolerability. Response to treatment was defined as a decrease in initial HAMD-17 score by 50%. Remission was defined as a HAMD-17 score of less than eight. The results aligned with the initial hypothesis supporting treatment outcomes using pharmacogenomic testing. The guided group of patients had a response rate of 50% compared to the unguided group at 36%. The pooled relative risk (RR) for treatment response comparing guided versus unguided treatment was 1.36 or a 95% confidence interval in favor of guided treatment and a ($p=0.0006$). The pooled RR for remission was 1.74 or 95% confidence interval and a ($p=0.02$) which demonstrates statistical significance. The remission rates of the guided treatment group were 40% when compared to the unguided

group at 25%. It was noted that different brand name of pharmacogenetic testing displayed different response and remission rates. NeuroIDgenetix and CNSDose showed a significant positive effect towards guided therapy whereas Genesight and Neuropharmagen did not show any difference between guided and unguided therapy. Some limitation noted in this meta-analysis were that multiple studies were funded by companies who manufacture the pharmacogenomic tests. Other things of note were that most studies were not blinded or controlled, the lack of heterogeneity, the use of different genotyping kits, and the small number of studies and inclusion of open-label cohort studies. All these aspects may potentially decrease the reliability of the reported results (Rosenblat, Lee, & McIntyre, 2018).

In a 12-week, double blind, parallel, multi-center randomized controlled trial by Perez et al. (2017), 316 adult subjects who were diagnosed with MDD were evaluated. The clinical global impression scale (CGI-S) was used to identify patients with a score greater than 4. The scale ranges from 1 meaning normal or no disease, to 7 which is related to the most severe form of disease. The trial evaluated how effective the use of PGx was when utilized in medication management for treatment of MDD. Randomization was used which either gave the prescribing psychiatrist access or no access to PGx results. The PGx utilized in this study was Neuropharmagen. There were 155 patients who received PGx guided treatment while 156 received treatment as usual. The endpoint of the 12-week study was to achieve a response that was sustained. Unfortunately, a sustained response was not seen within this study time frame with a ($p=0.4735$). Of note, the PGx guided treatment group did have a higher rate of response to medication at 47.8% compared to the TAU group at 36.1%. This demonstrated a ($p=0.0476$) with a 95% confidence interval. Patient who had previously attempted at least one medication for depression prior to this trial did have more positive outcomes. This is likely due to being

prescribed a medication that they have not tried in the past which decreased the room for error. Side effects were lower at six weeks and remained lower at twelve weeks for the PGx group as well. Limitations of this study included multiple patients who had previously failed one or more antidepressant therapies, therefore decreasing the odds on receiving an appropriate medication. Also, a longer study time may have been able to identify a sustained response to medication. The population size was also small, and a larger population may be needed to appropriately analyze results of such a study.

In an 8-week, single-blinded, and randomized clinical trial by Han et al. (2018), the effectiveness of PGx vs. TAU was evaluated in 100 Korean patients. All patients were randomly placed in either the PGx or TAU group. The patients were at least 20 years old and diagnosed with MDD by experienced psychiatrists using the DSM-5 for diagnosis criteria. Middle-aged, married, and unemployed women were the highest demographic in both groups. Patients with other psychiatric conditions were excluded from the study. Also, patient with substance abuse, neurological impairment, or pregnancy were not entered into the study. Inclusion criteria were: 1) Patients needed to currently be on antidepressant therapy for at least six weeks which included mono or polytherapy; 2) Patients needed to score a 3 or greater on the CGI scale; 3) Patients must be deemed intolerant to their current antidepressant use. All participants underwent saliva sampling prior to the study which was evaluated by Neuropharmagen which is a pharmacogenetic analyzing system. Complete medical/neurological examinations were completed on all patients prior to entering the study. Neuropharmagen was able to analyze 22 antidepressants, 13 mood stabilizers, 6 anti-anxiety medications, and 5 other neuropsychotropic drugs. They were categorized by colors, green being more likely for positive response, red likely for intolerance or negative response, yellow needing to be closely monitored, and white which

had no genetic variants discovered at that time. At the beginning of this study patients were randomized by a computer generator with a 1:1 ratio to be placed either in therapy guided by PGx or TAU. Based on randomization the patient was either placed on a PGx or a TAU medication based on medical history and provider preference. Patient's continued to take benzodiazepines and sleeping aides as usual. The primary endpoint was the mean change of the total score of the in 17-item Hamilton Depression Rating Score (HAMD-17) from the patient's baseline compared to measurement at the end of treatment. The secondary endpoint consisted of response and remission rates. Response was defined as a 50% reduction in HAMD, and remission was defined as a HAMD score of <7. Patients in both groups had a moderate to severe HAMD rating at the beginning of the study (23.8±4.8). The study began with 52 individuals in the PGx group, and 48 in the TAU group. The PGx group ended up with 39 completing the study and 30 in the TAU group completing.

Results of the study by Han et al. (2018) were in favor of pharmacogenomic testing with an increased change in the HAMD score in the PGx guided patients by a 4.1 difference ($p=0.010$). The response rate was substantially higher based on the HAMD in the PGx group compared to TAU with a 28.1% difference ($p=0.014$). The remission rate also reported higher with PGx guided therapy with a 19.9% difference, although did not prove statistical significance ($p=0.071$). Limitations were that the study was only single blinded which gives room for bias. The study was limited to each subject receiving one antidepressant even if an adverse event occurred, and the sample size was small.

In the open-label, eight-week study by Hall-Flavin (2013), pharmacogenomic testing was explored to see if gene guided medication management of MDD was beneficial. The open-label study was divided into two groups. In the first group (unguided), the pharmacogenomic profiles

were not provided to the treating clinician until the study was complete. In the second group (guided), the pharmacogenomic data was provided to the clinician to help guide medication decisions in the patient's treatment. Three depression screens were used in this study consisting of the HAMD-17, QIDS-16, and PHQ-9. Results were collected at baseline and then at weeks 2,4, and 8. The results demonstrated higher outcomes in the pharmacogenomic guided group based on the results of all three screening tools. Some of the participants in the unguided group were treated with medications that would not have been recommended according to the pharmacogenomic profile. As a result, this group yielded the lowest improvement in scores. Participants in the guided group with a medication congruent with their pharmacogenomic profile had the greatest improvement. HAMD-17 and PHQ-9 reached statistical significance with PHQ-9 ($p=<0.001$) and HAMD-17 ($p=< 0.001$). Not only did the scores decrease more with the guided group, but they decreased faster at 2,4, and 8 weeks. One limitation of this study was the high rate of participants dropping out of the guided group. This could have increased the number of participants scoring poorly on screening tools. Also, due to the design of the study, participants in the guided group knew the results of their genotyping which may have caused a placebo effect or influenced their scores. With that said, after eight weeks the guided group had a 10.9-point decrease in their HAMD-17 score compared to 6.5 of the unguided group. The 4.4-point difference exceeds the 3-point standard for clinical significance set by the National Institute of Clinical Excellence (Hall-Flavin, Winner, Allen, Carhart, Proctor, et. al 2013).

Cost Effectiveness of Pharmacogenomic Testing

An article by Maciel, Cullors, Lukowiak, & Graces (2018) was a review of two studies. The first is by Greenberg et al, (2015), and is titled "The economic burden of adults with major depressive disorder in the United States". The second is by Bradley et al. (2017) and is titled

"Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: a randomized clinical trial demonstrating the clinical utility". The annual economic burden of adults with MDD as studied by Greenberg was $30,949 compared to the control group at $5,744 in the year of 2012. This was measured in U.S. dollars. This analysis compared the costs that were associated with "red bin" patients (medications that are identified as problematic) to "green bin" patients (use as directed medications) and "yellow bin" patients (use with caution) based on the results of pharmacogenomic testing. The "green bin" guided group had a 1.21 net reduction in disability days per months which averaged a saving of $1,453.56 annually. The model showed a potential yearly cost savings of $3,962 per patient with guided treatment per NeuroIDgenetix after adding the $2,000 cost of the genetic testing. They measured the efficacy of treatment with pharmacogenomic guided treatment in a variety of settings outside of general psychiatric care. In conclusion, this model predicts an average savings of $3,962 per year in U.S. dollars when treatment is guided by pharmacogenomic testing. Some limitations are that the funding of initial studies is not known, the brands of genotype testing kit used, and unknown comorbidities of patients. The study by Bradley et al. had 685 participants in various settings. The researcher's results demonstrated a significantly higher remission rate of 35% versus 13% and ($p=0.02$) for the guided treatment group compared to the treatment as usual (TAU) group. There was also a much higher response rate with the guided group 73% versus 36%, ($p=0.001$) compared to TAU. Limitations include that the data published in peer reviewed journals where efficacy and cost effectiveness were evaluated by two different sources which may skew results. Also, quality of life is not taken into consideration while analyzing the noted studies.

The next study conducted by Peterson et al. (2017) looked at the efficacy, harm, and cost effectiveness of PGx versus TAU for MDD treatment. The study included two RCT's, five

controlled cohort studies, and six modeling studies. The modeling studies primarily focused on women in their mid-forties with few comorbidities. The RCT's and controlled cohorts focused on adults with MDD and allowed any manufacturer of pharmacogenomic testing kits to be allowed in the study. There was no restriction on timing of the study, settings, or design. Agency for Healthcare Research and Quality (AHRQ) was the guide used to measure the strength of the evidence as low, moderate, high, or insufficient. StatsDirect software was utilized to pool the gathered data using a random-effects model. Statistical heterogeneity was measure by a Cochrane's Q test. Multiple genotype testing kits were assessed including CNSDose, ABCB1, and Genesight. Response was measured as a 50% reduction in the HAMD score. Remission was achieved with a HAMD < 10. CNSDose was the only genotype test that significantly improved remission rates with one in every three tested remitting within 12 weeks. CNSdose also reduced the number of patients taking sick leave 15% versus 4%, (p=0.0272) and reduced medication intolerability with a 95% CI. ABCB1 also had one in three patients remitting in a shorter period of 5 weeks but did not account for tolerability, quality of life, functional status, and side effects of the medication and therefore was not found to be statistically significant. Genesight did not improve response or remission rates (CI=0.56) to a statistically significant value, nor was tolerability accounted for. Cost effectiveness is unknown, and evidence is low due to the low number of RCT's with a lack of directly observed financial saving. With pharmacogenomic testing for MDD treatment being in its early years of research, further studies will need to be completed to assess the potential costs or savings associated with this service. Although the study proved inconclusive, it does show somewhat promising results for CNSDose in the treatment and time of remission in patients with pharmacogenomic guided therapy. Limitations

include the number of RCT's reviewed, the small patient demographic, and the unknown comorbidities of selected patients.

In a study by Benitez, Cool, and Scotti (2018), the authors evaluated administrative claims by health plan members who were treated for psychiatric conditions with PGx vs. TAU. Costs were defined as any payment or reimbursement made for the treatment of psychiatric conditions which included depression, anxiety, bipolar, premenstrual dysphoric disorder, post-traumatic stress disorder, obsessive-compulsive disorder, and schizophrenia. This included prescriptions, office visits, inpatient, and outpatient services. They used a major healthcare insurance provider which consisted of over 25 million members. Payments were evaluated for 24 months, pre and post treatment. Although only records were reviewed, plan member records evaluated had to be at least 18 years old and on a commonly prescribed psychotropic medication starting within the past 180 days and without other known history of psychotropic medication use. These could be members who received TAU or PGx. Statistical significance was evaluated by measuring the pre and post treatment cost controlling demographics and comorbid conditions. They analyzed 205 members treated by PGx and 478 with TAU. There was no significant difference in the cohorts when age and gender were observed. Although over the period studied the healthcare costs in both groups did rise, the TAU increase was higher at $23,132 versus $17,627 ($p=0.0004$). The cost of the PGx test was taken into consideration during these analyses. It was noted that the reduced spending was mostly saved by a decrease in outpatient services received. Once broken down with a focus on depression, costs did continue to rise for both groups, but higher in the TAU group at $24,791 vs $18,741 ($p=0.0090$). This included 94 members with PGx and 229 with TAU. The savings were related to outpatient, inpatient, and pharmacy costs. Limitations of this study included not knowing the brand of PGx test being

utilized and no way of knowing if the prescribers followed the PGx recommendations since only the administrative claims could be reviewed. The course of treatment was also not well known.

Discussion

These studies have shown some promise in the use of pharmacogenomic testing for the treatment of MDD. MDD may affect a person in many different aspects of their life whether it be emotionally, physically, or financially. As the use of pharmacogenomic testing in the treatment of MDD continues to be explored, the very complicated disease process of MDD that may stem from multiple variances in genes must be considered. After reviewing the literature, the use of PGx may have a positive impact in the treatment of MDD when compared to TAU. As advances continue, this will help guide treatment and reduce the cost associated with the treatment and management of MDD.

When comparing the studies on effectiveness of PGx guided treatment, response rates were higher in all studies for the guided therapy groups. Also, remission was higher with guided therapy, but in most studies, remission was not sustained due to the short study periods being analyzed.

Pathophysiology of Major Depressive Disorder

In the articles discussing the pathophysiology of MDD, it is a common theme that neurogenesis and genetic biomarkers play a role in the development and/or progression of MDD. Although this can be agreed on, the exact science of different biomarkers along with environmental factors remains an area of uncertainty. Continued research will reveal different mechanisms that play a role in the disease process.

In the meta-analysis by Verdujin et. al (2015) no link between BDNF and MDD was established, but in contrast, the review by Villanueva (2013) discussed the link between low serum BDNF and MDD. Further investigational studies are needed to assess this more thoroughly.

Also, the lack of studies in this project which address lifestyle/environmental factors contributing to the diagnosis and/or progression of this disease makes it hard to fully evaluate all components that may lead to MDD.

In patients with major depressive disorder (MDD), are medications guided by pharmacogenomic testing in the treatment of major depressive disorder more effective in achieving response and remission of symptoms compared with TAU based on depression assessment scales?

The articles evaluated showed positive outcomes in many aspects of treating patients with pharmacogenomic guided treatment. In the article by Rosenblat, Lee, and McIntyre (2018), the study did replicate the hypothesis that the effects of PGx would have more favorable outcomes when the patients pharmacodynamic and pharmacokinetic profiles were known by the provider prescribing the medication. They also noted that in many studies patients who are aware of PGx may have an enhanced placebo effect because they feel that they are getting the best possible medicine to treat their disease. Their analysis did overall favor PGx with reported higher response and remission rates as seen in table 1 and table 2.

In the open label study by Hall-Flavin et al. (2018) they discussed the key elements that would be required to make an impact and possibly change the way psychiatric care is delivered. The three key elements were “(a) pharmacogenomic information must be predictive of those individuals whose specific treatments are likely to be intolerable or no efficacious; (b)

pharmacogenomic information must be easily integrated into clinical workflow; (c) it must effectively guide treatment decision, resulting in improved clinical outcomes" (p. 543-544). In this study by Hall-Flavin et al. (2018) all three elements discussed above were met. This is a great success for the future of pharmacogenomic testing in the psychiatric world.

Given that most of the studies reviewed were conducted over 8-12 weeks, Perez et al. (2017) notes that longer follow up times in these studies may help confirm that response to medication is sustained. As many of these medications take weeks to be effective, it is hard to judge if the response is sustained in such a short time frame. The study by Hall-Flavin et al. (2018) did discuss how placebo affect could influence an earlier response which would be seen in these shorter timeframes.

In an article by Kitzmiller, Groen, Phelps, & Sadee (2011), the importance of gene testing for multiple scenarios was discussed. For example, patient with the polymorphism 5-HT 2A should receive Citalopram for their treatment due to higher reported side effects from different SSRI's. This is just one instance of progress being made in this new field of research. With that said, the study by Hall-Flavin et al. (2018) demonstrated that the guided treatment group had more CYP2D6 poor metabolizers than did the TAU group. The significance of metabolizers in the PGx versis TAU groups may skew results based on the treatment group in which they fall into.

It is important to remember that genes are not the only variability that could affect the tolerability of a medication. According to Perez et al. (2017), the response and tolerability may be affected by multiple other aspects of the patient such as medication-medication interaction, lifestyle, drug use, and other environmental factors.

The article by Fabbri & Serretti (2015) evaluated genes such as SLC6A4, HTR2A, BDNF, GNB3, FKBP5, ABCB1, and the cytochrome P450 system whereas the study by Verdujin et. al (2015), looked at the involvement of different pathophysiological mechanisms such as inflammation, hypothalamic-pituitary axis, neurotrophic factors, and vitamin D. When evaluating the effectiveness of PGx, we can see it is important to know what is being measured as different studies have evaluated different pathophysiology of the disease.

According to Rosesnblat, Lee, & McIntyre (2018), it is important to remember that these studies only reported "proprietary pharmacokinetic polygene pathway pharmacogenetic interpretive formula" (p-488). As this field continues to grow it will be important to look at other genetics such as CYP450, serotonin receptor, transporter genes, and p-glycoprotein genes. This will only help to improve the efficacy of pharmacogenomic testing and hopefully help bring it to the forefront of psychiatric care. This article again focused on the complex nature of PGx testing which was outlined in other articles as mentioned above.

In the meta-analysis performed by Rosenblat, Lee, and McIntyre (2018), the PGx Neuropharmagen did not demonstrate a statistically significant difference in response or remission rates vs. TAU, whereas the 12-week, double blind, parallel, multi-center randomized controlled trial by Perez et al. (2017) demonstrated statistically significant results with treatment guided by PGx vs. TAU. Therefore, it is important to remember that the limitations of these studies may have a profound effect on the outcome and that the lack of homogeneity between different PGx which may demonstrate much different results.

According to Han et al. (2018), one must consider that over 40 pharmacogenomic testing kits are available for use. They go on to note that many of the recommendations from the four different PGx kits that were used in their trial had substantial differences in what genes and

variants were tested. The algorithms to predict the drug-gene interactions were also noted to be quite different. With the noted results above, continued studies on efficacy of certain PGx kits must be evaluated. The importance of reproducibility will greatly impact the likelihood of psychiatrists and providers acknowledging these products as reliable and accurate. With that noted, the results were supportive of increased response and remission rates with the use of PGx testing as seen in table 1 and table 2.

In an article by Ikediobi, Shin, Nussbaum, & Phillips (2009), the knowledge clinicians have about pharmacogenomic testing has a significant influence in the ability to make the integration of this practice into the clinical setting successful. Many clinicians are currently not comfortable or confident with the use of such testing, therefore as studies continue to show positive outcomes, educating providers must occur in order to optimize outcomes of patients diagnosed with MDD.

It is clear the lack of education regarding PGx guided treatment within the healthcare community continues to slow the process of mainstreaming this new tool into clinical practice. While multiple studies continue to demonstrate the improvement of response and remission of MDD with the use of PGx, we should continue to see this instrument show a greater presence in everyday healthcare. PGx treatment in cancer has shown great promise and with continued success it will be one of the most useful tools in treating MDD.

In patients with MDD, does medication management guided by pharmacogenomic testing improve cost effectiveness in the management of disease compared to TAU?

In the study by Benitez, Cool, & Scotti (2018), the cost savings of PGx could be substantial in patients with complex comorbidities as well as polypharmacy issues. Guiding treatment to decrease side effects and increase tolerability while considering comorbid diseases

and other medications utilized can prevent hospitalization, outpatient follow-ups, and pharmacy costs.

In the article by Kitzmiller, Groen, Phelps, & Sadee (2011), when providers have access to the status of their patients' genetics, being able to predict response to medications becomes more feasible which in turn leads to better drug efficacy, fewer side effects, and a better cost to benefit ratio.

According to Han et al. (2018), the economic benefits of PGx should be considered as an important factor while implementing this new tool into clinical practice. With the favorable results of his study and multiple other meta-analyses, substantial reduction in healthcare spending could be seen by utilizing this technology.

According to Groessl, Tally, Hillery, Maciel & Garces (2018), a large portion of patients do not respond to initial treatment prescribed for MDD and have decreased productivity and a higher rate of suicide. The trial and error of treatment as usual can delay proper care by days, months, or even years. The delays can be directly related to an increase in patients suffering, higher medical costs, and a higher risk of suicide. Being able to possibly identify a medication that may be effective is critical in decreasing the cost of healthcare that grows as a patient continues to struggle with MDD. Groessl, et al. (2018) states, "growing evidence supports the use of pharmacogenetic-guided treatment to shorten the length of time required to identify an effective treatment regimen" (p.731). Their study also evaluated care over three years which identified reduced costs associated with treatment of MDD as well as higher effectiveness.

Although many different variables must be taken into consideration when looking at the cost effectiveness of PGx in the treatment of MDD, the above studies have demonstrated multiple scenarios with improved economic impact when utilizing this service. Replication of

studies with similar results should help pave the way to moving forward with the implementation of PGx guided treatment into mainstream medicine.

Currently many commercial insurances do not cover any form of pharmacogenomic testing for the treatment of MDD. Current medical practices continue to rely on TAU and provider preferences, but continued research and studies of MDD should help move this new practice forward.

Applicability to Clinical Practice

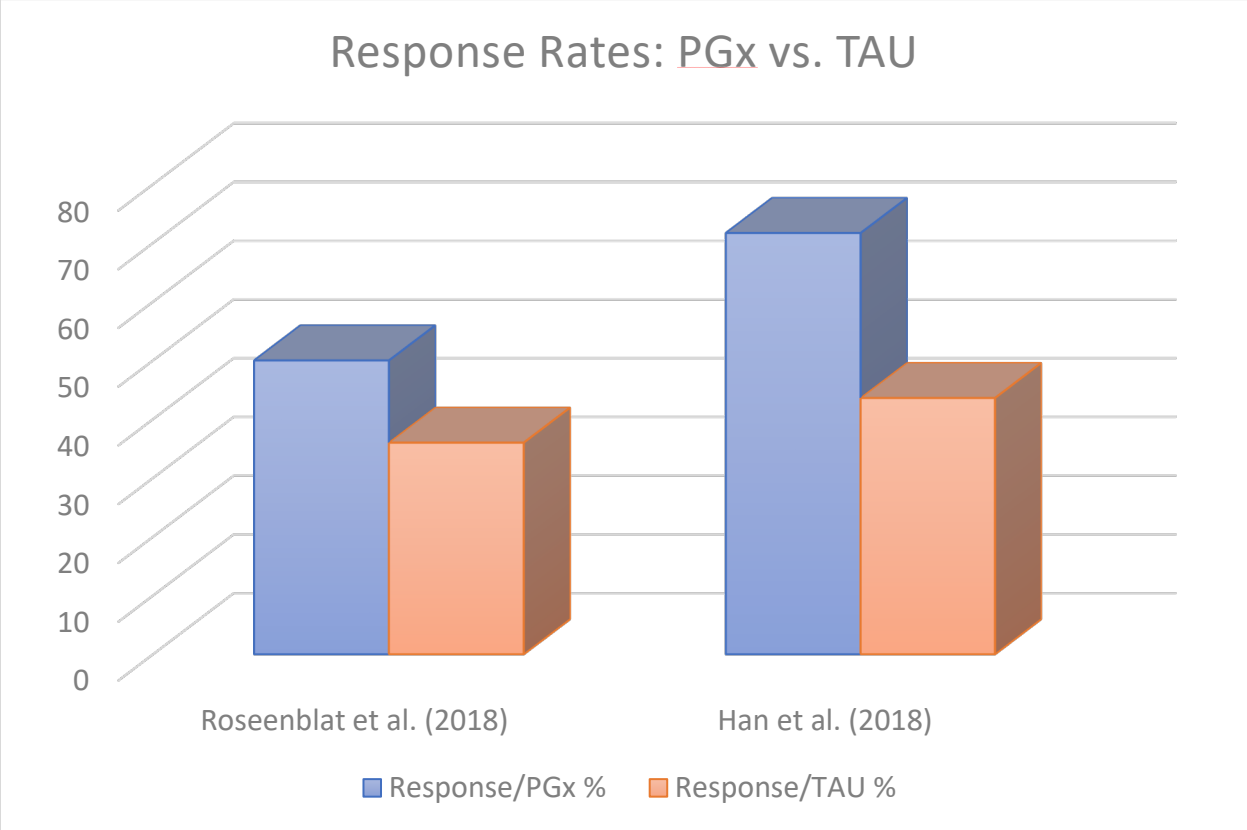
The goal of this project was to evaluate the use of pharmacogenomic testing in the treatment of MDD compared to TAU. Another goal was to also evaluate the cost-effectiveness of PGx. As we strive to make mental health topics less taboo, the treatment of these diseases will surely increase. With new advances such as PGx, genetically guided treatment will continue to be evaluated and hopefully show positive outcomes for those suffering from such conditions.

Treatment of MDD can be quite challenging whether it be by psychiatry or family medicine. Being able to review an individual's genetics and how they may react and/or metabolize a drug should eliminate time and cost while improving the patient's mental health. Many of these studies show that utilizing PGx has shown greater improvement in depression rating scores, less cost associated with treatment, and improved quality of life.

Exploring and testing the effects of BDNF, cortisol, inflammatory markers, and Vitamin D levels have revealed some common links between a person's health and MDD. As PGx continues to evolve it is likely that we will see more studies evaluating the CYP450 system to better understand the metabolism of many of these drugs. As some insurance companies are now covering some or all costs of these tests, it is presumed that they will become more readily available and providers will receive proper education on the utilization of PGx.

Table 1.

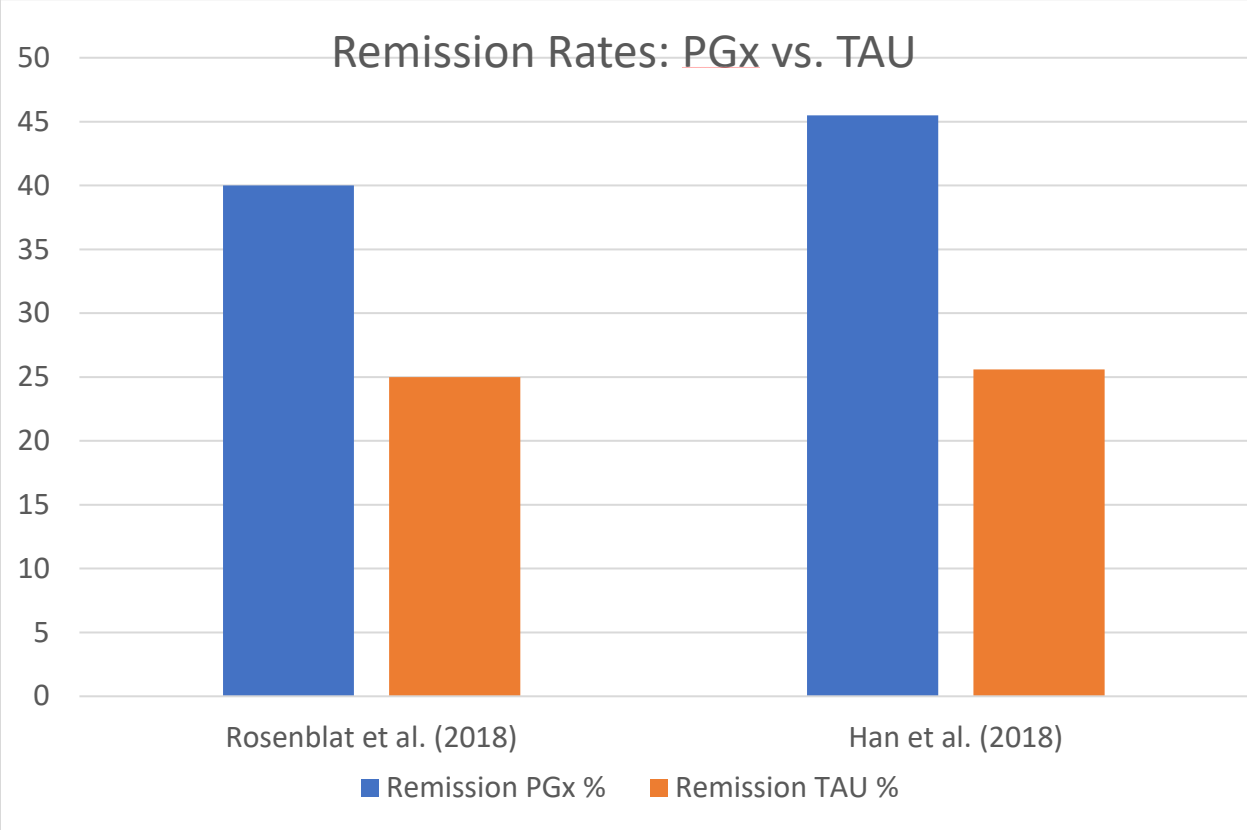
Response rates of PGX vs. TAU in the treatment of MDD



Note: Data for this chart came from Rosenblat, Lee, and McIntyre (2018) and Han et al. (2018).

Table 2

Remission rates of PGx vs. TAU in the treatment of MDD



Note: Data for this chart came from Rosenblat, Lee, and McIntyre (2018) and Han et al. (2018).

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