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THE IMPACT OF BONE MARROW TRANSPLANTION ON PATIENTS WITH PSYCHIATRIC DIAGNOSES: MEDICATION ADHERENCE ASSESSMENT

Brittany Galop
University of Kentucky, brittany.galop@uky.edu
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Brittany Galop, Student

Dr. Dave Feola, Major Professor

Dr. Dave Feola, Director of Graduate Studies

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THESIS

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science in the
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By

Brittany Nichole Galop

Lexington, Kentucky

Director: Dr. David Feola, Professor of Pharmacy

Lexington, Kentucky

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ABSTRACT OF THESIS

THE IMPACT OF BONE MARROW TRANSPLANTION ON PATIENTS WITH PSYCHIATRIC DIAGNOSES: MEDICATION ADHERENCE ASSESSMENT

We investigated whether there is a measurable difference in medication utilization for psychiatric conditions before and after bone marrow transplantation (BMT). Previous studies have identified a potential association between psychiatric conditions and immune function. We hypothesized that medication utilization for psychiatric diagnoses would be impacted by BMT. This study was a retrospective, quasi-experimental cohort design. Two measurements of medication utilization, proportion of days covered (PDC) and medication possession ratio (MPR) were calculated for each included Medispan-defined class of medications before analyzing changes in PDC and MPR at the patient level. There was a statistically significant decrease in the number of raw prescriptions as well as in PDC value in the 2 years after BMT as compared to before the procedure. We found a decrease in medication utilization after BMT across the measured medication classes, indicating a potential resolution of psychiatric symptoms and a potential impact on the associated pathophysiology. These results provide support for the premise that genetic factors associated with immune function play a role in psychiatric illness.

KEYWORDS: bone marrow transplant, psychiatric conditions/diagnoses, psychiatric medications, medication adherence

Brittany N. Galop

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By

Brittany Nichole Galop

Dr. David Feola
Director of Thesis

Dr. David Feola
Director of Graduate Studies

05/11/2020

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Section One: Introduction

Overview

Current healthcare practices require disease states to be assessed through objective assessments and clearly documented outcomes associated with the present condition.[1] Psychiatric conditions, however, are not assessed in this manner. Despite 4.5% of Americans suffering from a serious mental illness (equaling 11.2 million people), patients diagnosed with mental health conditions have a higher difficulty being able to receive treatment.[2] The underlying cause of delays in receiving treatment include lack of objective diagnostic tests, a paucity of clinical trial data due to the amount of time required for medication trials, and the patients' overall wellbeing adversely affecting their ability to consistently follow treatment plans. Consequently, patients contend with increased hospitalizations, higher likelihood of polypharmacy and a lower quality of life.

Difficulties in identifying diagnostic tools have led researchers to explore different genetic components that may be either associated with psychiatric illnesses or potential treatment options for these patients. Over the past decade, researchers have utilized genetically altered mouse models in order to uncover the role of previously understudied genes and genetic markers. Of particular note, mice that lack the *Hoxb8* gene, which was thought to be associated only with the production of microglia during gestation, display psychiatric tendencies primarily associated with obsessive-compulsive disorder (OCD).[3] Interestingly, this behavior is reversed by bone marrow transplantation (BMT), suggesting that there is an immune component to psychiatric pathophysiology.[4] Genome-wide associated studies (GWAS) have found additional associations between genes expressed by the immune system and schizophrenia. Upon further investigation, case reports have shown a similar relationship for patients receiving allogeneic bone marrow transplantation and reduction of psychiatric symptoms. The work presented in this thesis investigates the relationship between the immune system and psychiatric illness through the evaluation of medication use before and after allogeneic BMT.

Psychiatric Conditions and Difficulty in Effectively Diagnosing and Treating

Unlike other disease states, psychiatric conditions do not have objective laboratory measurements and standardized diagnostic tests to pinpoint a diagnosis. Consequently, the average time between first symptoms and diagnosis is approximately 11 years.[5] This delay is primarily due to the subjective nature of diagnosing psychiatric conditions — clinicians must rely primarily on interpreting symptoms instead of proof of a primary cause. Scoring systems are utilized in diagnosing psychiatric conditions and consist of a review of patients' self-reported symptoms that may or may not meet criteria for a specific diagnosis. These scales are diverse, generally being condition-specific in use and following different classifications depending on what governing board has established and applied the specific scoring system's use.[6] Common scales include Comprehensive Psychopathological Rating Scale (CPRS), Global assessment of functioning (GAF), Major Depression Index (MDI), Positive and Negative Syndrome Scale (PANSS), and Generalized Anxiety Disorder 7 (GAD-7).[6] Without an appropriate diagnosis, patients suffer from decreased quality of life and increased symptoms that lead to more frequent hospitalizations and/or worse outcomes.

Primary diagnostic tools utilized for mental health patients generally follow the international guidelines called the Diagnostic and Statistical Manual of Mental Disorders (DSM), currently in its 5th edition.[7] These guidelines outline specific psychiatric conditions and diagnostic criteria based on the scale of common symptoms associated with the corresponding diagnosis. This set of guidelines provides a more in-depth analysis of symptoms for each disease state and is the primary assessment of most psychiatric conditions. The DSM-V has been assembled by mental health specialists and also provides updates according to what may change in current practice. The DSM is regarded as reliable with clinicians understanding to use social sciences that may apply to their specific patient more than those outlined in the guidelines.[8]

In addition to the difficulty in diagnosing patients with psychiatric conditions, extensive time and effort is required to find effective treatment regimens. The average period to optimize a patient's appropriate long-term treatment is three to five years.[5] This delay is the result of the prolonged amount of time psychiatric medications require to

reach steady-state, the myriad of adverse effects associated with these medications, and ultimately the patient's ability to continue therapy on their own.

Patients categorized as having a serious mental health disorder have the most difficult time with therapy management compared to patients with other mental health diagnoses.[5] Serious mental health disorders are defined as those that are treatment-resistant or those that cause debilitating diseases including schizophrenia, obsessive-compulsive and/or other spectrum disorders.[4] In fact, it was found in 2018 that only 64.1% of patients with serious mental health disorders receive treatment for their illness and that treatment-resistant patients account for 85% of mental health associated hospitalizations.[9]

This patient population struggles with normal day-to-day operations due to debilitating symptoms that may lead to delirium, psychosis or extreme fatigue. Because of decreased ability to focus on daily tasks, many times these patients struggle with adhering to their medications, leading to worsening symptoms that require hospitalization or institutionalization.

Cost is a primary concern for all aspects of care, with hospitalizations responsible for a large component.[10] In Table 1.1, the average cost and length of hospitalized stay (LOS) for acute disease exacerbations of a variety of diagnoses are depicted.[11] This data demonstrates that patients with schizophrenia typically are subject to lengthy stays that carry significant cost. Although cost during their hospitalizations may not be as high for patients with mental health conditions as those with certain cancer or infectious disease diagnoses, the average LOS was higher for schizophrenia and other serious mental health conditions.[10,12]

Table 1. 1 Hospitalization Average Length of Stay and Cost for Chronic Conditions[11]

Diagnoses	Average LOS	Average Cost
Acute bronchitis	3.1	$10 917
Bacterial infection, unspecified site	7.1	$33 073
Congestive heart failure, nonhypertensive	5.3	$29 842
Diabetes mellitus without complication	2.7	$9 455
Multiple myeloma	10.2	$56 584
Schizophrenia and related disorders	11.5	$20 510
Substance-related mental disorders	4.9	$10 715

Patients with mental health disorders not only struggle with acute exacerbations, but additionally many patients are uninsured or covered by Medicare. Table 1.2 shows the impact of mental health diagnoses to both Medicare and other systems that provide care to the uninsured. This data emphasizes the financial burden created by the ongoing care of these patients and what may take place with exacerbated symptoms leading to hospitalizations. Finding any objective biomarker for healthcare professionals would revolutionize the diagnosis and treatment of patients with psychiatric diagnoses, resulting in increased patient treatment success, fewer hospitalizations and decreased costs. While

longitudinal counseling, behavioral intervention and pharmacotherapy can provide efficacious long-term management, these treatments are not curative. Advancing our knowledge of the underlying genetic components of mental health disorders is critical and could lead to treatment advances that are transformative to both individual patients and to our overburdened healthcare system.

Table 1. 2 Psychiatric Conditions and Average Cost with Associated Hospital Length of Stay (LOS)[9]

Psychiatric Diagnosis	Medicare Cost (average LOS)	Uninsured Cost (average LOS)
Schizophrenia	$8 509 (11 days)	$5 707 (7.4 days)
Bipolar Disorder	$7 593 (9.4 days)	$4 356 (5.5 days)
Depression	$6 990 (8.4 days)	$3 616 (4.4 days)
Drug Use Disorder	$4 591 (5.2 days)	$3 422 (3.7 days)
Alcohol Use Disorder	$5 908 (6.2 days)	$4 147 (3.8 days)

Medication Use in Patients Diagnosed with Psychiatric Illnesses

Most psychiatric diagnoses require pharmacologic intervention as a major component of therapy. Assessing a patient's medication utilization is a method for healthcare professionals to not only measure the patient's adherence to their therapy but

also evaluate the effectiveness of the medication in treating the condition.[13] Appropriate medication use, referred to as adherence, has extensive implications for patient care. Proper medication adherence can increase a patient's quality of life while decreasing hospitalizations.[13] In fact, non-adherence accounts for approximately 50% of treatment failures, 25% of hospitalizations and 125,000 deaths annually.[14,15]

Patients with mental health illnesses struggle with medication management and adherence to a greater extent than the general population. Table 1.3 depicts the medication adherence percentages of common mental health conditions.[16] These are considerably lower and more variable when compared to adherence rates for common conditions including hypertension (50-70%), congestive heart failure (40-60%), diabetes mellitus (approximately 35%), and patients taking oral antibiotics for skin infections (57-78%).[17-20]

Table 1. 3 Psychiatric Diagnoses and the Associated Adherence Percentages

Psychiatric Diagnosis	Adherence Percentages
Anxiety Disorders	57%
Major Depressive Disorder	28-52%
Bipolar Disorder	20-50%
Schizophrenia	20-72%

These lower adherence rates compared to other conditions are likely due to the difficulties that patients with severe mental health disorders experience, such as their inability to complete daily tasks. This statistic also emphasizes the necessity to find a way to assist patients with mental health diagnoses in managing their diseases more efficiently.

Nonadherence affects mental health patients in a variety of ways. One systematic review of antipsychotic use in bipolar and schizophrenic patients summarizes results from 38 studies consisting of 51,796 patients. The primary objective was to assess which factors contributed to non-adherence and the degree to which each was associated. For both bipolar and schizophrenic patients, it was found that substance abuse, cognitive impairments, a lower level of education, poor therapeutic alliance, high intensity of delusional symptoms, and low socioeconomic status were associated with poor adherence. To help overcome some of these barriers, this review found that building a personal relationship with the patient, providing more patient education and giving assistance in overcoming substance abuse led to increases in antipsychotic adherence and minimization in symptoms.[21]

In a study of 87 patients suffering from schizophrenia, overall self-reported adherence and potential factors that impacted that adherence were examined. Of the 87 patients, adherence was reported at approximately 50% with primary reasons for lower adherence being patients with lower insight and previous treatment-related trauma. This assessment demonstrates what many mental health patients struggle and provides context as to the importance of focused interventions in addition to medication therapy options.[22] Similar to the study described above, meta-analysis of schizophrenic patients found that non-adherence primarily stemmed from a lack of understanding, medication beliefs and substance abuse. In these patient populations, this nonadherence also led to increased risk of relapse, increased hospitalizations and suicide.[23] Patients who exhibited increased adherence also had better relationships with their healthcare staff as well as a better overall understanding of the medication benefits.[23]

Bone Marrow Transplantation and the Impact on Mental Health

Bone marrow transplant (BMT), also known as hematopoietic stem cell transplants (HSCT), is primarily used for the treatment of hematological malignancies.[24] The process includes introducing healthy hematopoietic stem cells (usually collected from the bone marrow) into a patient after eradication of the patient's own bone marrow through irradiation and chemotherapy.[25] A BMT is either allogeneic or autologous. Autologous transplants collect, purify and re-introduce the primary patient's own cells back into the body. Allogeneic transplants utilize donors who have matching human leukocyte antigens (HLA), which generally may include a matched family member, unrelated matched donor, or a family member with mismatched alleles referred to as haploidentical (more rare and higher likelihood for post-treatment difficulties).[25] The result of an allogeneic transplant is that an entirely new immune system is established by the donor stem cells.

BMT therapy has many complications due to its rigorous process. Regardless of the type of BMT, this "survival treatment" includes chemotherapy, irradiation and the long-term period of isolation in a germ-free unit. Complications can range from neutropenia, sinusoidal obstruction syndrome (SOS), and mucositis, to graft versus host disease (GVHD) and death. Additionally, these complications following therapy may be acute (within 90 days) or chronic (greater than 90 days). A 2010 study found that approximately 30% of patients survived five years after BMT. Those who did survive five years, however, had an additional 15-year survival rate of 80%.[26] Most mortality, however, is a result of the underlying malignancy and not the BMT itself.

Because our objective was to determine whether genetic factors of the immune system have a role in psychiatric pathophysiology, the fact that BMT can itself impact psychiatric disorders, primarily due to trauma associated with the therapy, is a complication of our design. One study showed that approximately 40% of BMT patients develop a clinically significant psychopathological disorder.[27] The study assessed the process of BMT and the potential induction of mental health disorders on both non-diagnosed and previously diagnosed mental health patients due to the physical and psychological stress that is exerted throughout the treatment. The two primary disorders induced or exacerbated were depression and anxiety. These cases, however, were mostly

in patients who had a relapse of their cancer following their BMT, or in those receiving chronic prednisone therapy.[27] Though the study seemed to show a large portion of patients with this concern, further investigation revealed it to be more concentrated in a patient population with these specific complications. Additionally, most patients resolved from the associated symptoms within 2-3 months post-BMT, thereby not leading to the requirement of a chronic mental health diagnosis.[3]

BMT has also been postulated to cause post-traumatic stress disorder (PTSD), depression, and anxiety. In a single-center study that was conducted in 37 female patients that were newly diagnosed with breast cancer, patients were assessed for the incidence of anxiety, depression or PTSD, and when it occurred during their cancer progression and treatment timeline.[28] The study used a symptom assessment scale, the Profile of Mood States (POMS), which includes multiple psychiatric conditions, though focusing on PTSD. One group of breast cancer patients underwent BMT following chemotherapy and was compared to a secondary group that only received chemotherapy and/or surgical interventions. Patients underwent the evaluation at initial diagnosis, initial treatment, recurrence of cancer (if applicable), BMT (if applicable) and at follow-up visits at 3, 6 and 12 months.[28] Incidence of PTSD was comparable among groups at time of diagnosis, and temporary phases of anxiety and/or depression were noted to occur throughout treatment. The patients who underwent BMT did not have higher rates of any symptoms except for a slightly elevated confusion score. Although this study had a smaller patient population, it provides an analysis of the impact of cancer on mental health distress, and that these outcomes are not significantly impact by BMT therapy.[28]

In recent years, healthcare teams have begun to assess patients' mental health state prior to BMT to assess their overall wellness and a patient's ability to successfully complete such a rigorous therapy. Many oncology teams utilize the National Cancer Center Network (NCCN) distress thermometer (DT) prior to BMT to evaluate a patient's stress level and ability to cope with such a procedure.[29] In a single-center study, 50 patients were assessed for mental distress prior to their BMT therapy. These patients were assessed using the NCCN DT, the Hospital Anxiety and Depression Scale (HADS), and the Coordinating Rating Scale (CRS) to assess patients' readiness for BMT.[29] This study found that 51% of patients had a statistically significant distress level of anxiety or

depression. The study also found that healthcare professionals underestimated the number of patients struggling with depression and/or anxiety associated with BMT.[29]

Because patients diagnosed with psychiatric conditions struggle with adherence, there is concern in whether or not patients with psychiatric diagnoses are able to effectively complete BMT therapy. One previous study was conducted to determine what the general effects of BMT were on patients that had a prior psychiatric diagnosis.[24] The study followed seven patients with leukemia who were also previously diagnosed with psychiatric conditions ranging from bipolar mood disorders and autism spectrum disorder to schizophrenia and borderline personality disorder. Of the seven patients, all were able to complete treatment with the exception of one patient diagnosed with borderline personality disorder. All others were able to successfully complete the BMT treatment with little to no adverse effects related to their psychiatric illness.[24] It was found that patient comprehension, proper psychotherapy before, during and following treatment and proper pharmacotherapy led to positive results with minimal adverse psychiatric effects. Additional studies noted that BMT in borderline personality patients was difficult to complete.[30] Treatment failure seems to be associated with the patient's ability to first comprehend the treatment, but then later exhibit changes in comprehension or acceptance of the treatment plan as their thought processes cycle between multiple personalities. The patient's physical and emotional wellness, however, is not typically hindered by the process of BMT induction, treatment, or follow-up.[24]

In summary, BMT can provide positive outcomes for those with or without prior psychiatric diagnoses. The BMT process induces minimal adverse effects related to psychiatric conditions.[24] As we use medication adherence measurements as a determinant of psychiatric disorder severity and response, it is important to consider these previous studies and characteristics of the impact of BMT itself on the mental illness.

Hoxb8, Microglia and Potential Mechanistic Explanations

Studies using mouse models have assessed a specific genetic variant that may contribute to changes in the immune system that could be associated with psychiatric conditions. The gene components most studied is the *Hox* gene group and specifically *Hoxb8* (OMIM *142963).[4,31] The *Hox* genes primarily function to provide

positional values in axes of the embryo, aiding in development. The protein encoded by *Hoxb8* is involved in the differentiation of myeloid progenitor cells into microglia for functions within the brainstem.[4]

Microglia function as the immune cells of the brain, having multiple purposes within the central nervous system. They act as macrophages by regulating foreign bodies access, responding to invasive pathogens by phagocytosing and killing them, and initiating inflammatory responses to infection and other traumatic processes.[22] The microglia also assist as dynamic contacts with synapses and may represent a stabilization and management system for neuronal cells.[4] When the number of microglia is decreased in the brainstem, the corticostriatal circuit is affected, causing abnormalities including frontal cortical synaptic expansion and striatal synaptic contraction. These changes lead to problems such as excess dendritic spines, pre-and post-synaptic structural changes, and long-term potentiation defects.[32] Deficits primarily seen with structural changes to synapses and dendritic spines involved decreased neurocognitive functioning similar to those who suffer from Alzheimer's disease, sever schizophrenia and/or autism spectrum disorder.[33]

Mutation of *Hoxb8* that inhibits functional protein production in mice induces an OCD-like behavioral phenotype. The two primary mutations of note at this time are a nonsense mutation of the first exon and a frameshift mutation in a premature translation stop codon that could lead to the complete alteration or removal of Hoxb8.[3] Mice that lack *Hoxb8* display uncontrollable grooming of not only the individual mouse but also of its cage mates. This behavior is thought to be due to a potential change in cognitive function as well as the loss of spinal cord sensory function.[4] These mutant mice were observed to spend an average of one hour less sleeping than the control group to focus on grooming, leading to excessive hair removal and skin lesions.[3] In addition to excessive grooming, these mice also exhibited hyper-anxiety and social behavior issues. Symptoms were difficult to resolve. In one study, knock-out mice were treated with fluoxetine, a selective-serotonin reuptake inhibitor indicated for the treatment of depression and OCD. The drug provided a resolution of the hyper-anxiety and social behavior issues but did not impact the excessive grooming behavior.[27] The study led investigators to hypothesize that the absence of functional *Hoxb8* was associated with obsessive compulsive behaviors.

Through further studies of *Hoxb8* deficiencies and its effect on OCD tendencies in mice, it was found that the only way excessive grooming behaviors could be reversed is through a bone marrow transplant from a healthy mouse.[4] This adoptive transfer of normal bone marrow to rescue *Hoxb8* function and eliminate OCD tendencies shows the potential pathologic involvement of immune function associated with OCD. Therefore, it is hypothesized that other psychiatric conditions may also be affected by the immune system and that a change in said function through BMT could alter psychiatric conditions.

Since activity was noted in the central nervous system, researchers then wanted to determine whether *Hoxb8* had a role in affecting nociceptive (pain) receptors and cognitive function in addition to the impact on behavioral.[34] A study analyzed knock-out mice that had healthy Hoxb8 removed in order to then see if both spinal cord function as well as induced OCD tendencies would be reversed.[4] They found that when the *Hoxb8* gene was removed only from the hematopoietic system, it led to excessive grooming but no spinal cord sensory defects.[4] Investigators then re-introduced healthy *Hoxb8* genes into the mice. This led to hair regrowth on the previously exhibiting excessive grooming mice over five months, with four of the ten mice making a full recovery and becoming indistinguishable from the wild-type mice.[4]

These studies help to differentiate behavioral symptoms from pain pathways and also pinpoint the hematopoietic system as an area of intervention to improve behavioral symptoms, but unable to restore cognitive function.[4] A secondary study also reviewed this theory and found that knock-out mice with mutated Hoxb8 showed no skeletal, forearm clasping or dorsal root ganglia defects leading to a focus on the treatment of behavioral changes for the mice.[3] Consequently, BMT produced some positive outcomes such as the reversal of excessive grooming behaviors. Nociceptive and spinal cord defects, however, were not able to be reversed if observed prior to transplant.

Additionally, some researchers have hypothesized that the *Hoxb8* gene is only involved in the embryonic phase of life, with no involvement in adult species. RT-PCR assays, however, confirmed that the *Hoxb8* gene was not only expressed in embryonic development but also in adult mice.[27] In adult mice, the effects of *Hoxb8* were further analyzed through functional imaging studies to determine where in the brain may be

associated with changes in *Hoxb8*. The results showed that *Hoxb8* was present in the basal ganglia and neocortex, which are primarily involved in the OCD circuit of the brain function.[3] These results associate *Hoxb8* gene expression and behavior issues in mice and suggests a potential association with human trichotillomania or OCD.

When reviewing these studies, it is valuable to understand the similarities and differences of OCD and trichotillomania (TTM). Trichotillomania is primarily known as repetitive hair-pulling that leads to noticeable hair loss.[35] This repetition is due to an uncontrollable urge and instant gratification associated with impulsivity, whereas OCD is more focused on obsessive thoughts that lead to ritualistic behaviors.[35] Though the two are similar in regards to symptomatology, it was found that OCD has a much higher incidence of lifetime disability whereas TTM may be managed over a shorter period of time. Additionally, TTM has a lower response rate to treatment which makes the disease more difficult to evaluate by examining medication use.[35] In the studies described above, the primary diagnosis observed in mouse models was obsessive-compulsive disorder, although components of TTM were acknowledged and considered on the spectrum of OCD.[31]

Case Reports

The studies conducted in animals described above provide compelling evidence that genetic mutations in immune genes could be associated with psychiatric illness. However, no controlled trials exist that address this hypothesis in humans. Data is limited to a case series and a few case studies that provide anecdotal support. A study is being conducted in which investigators have requested records from cases involving BMT and coincident schizophrenia. Thus far, they have collected data for 22 patients over the course of 15 years with schizophrenia prior to BMT that also had an autoimmune diagnosis.[36] For the patients currently included, the post-BMT results included reduced symptoms associated with both schizophrenia and their autoimmune diseases. The reduction of symptoms is being assessed through reviewing treatment use, which decreased for all patients following their BMT procedure.[36] This study has laid the groundwork to assess more patients diagnosed with psychiatric conditions undergoing BMTs and in order to evaluate its impact on long-term outcomes.

There is little to no information regarding patients undergoing a BMT and having reversal of symptoms associated with their psychiatric diagnosis. The only documented incident of this phenomenon took place in 2009. A treatment-resistant schizophrenic patient underwent a BMT to treat acute myeloid leukemia.[37] Before his BMT procedure, the patient's treatment regimen included quetiapine, risperidone, and olanzapine. The patient suffered from delusions and hallucinations that continued to be refractory to these therapies. He was deemed appropriate for BMT as a part of his AML treatment and went through 34-day isolation and had a rigorous follow-up treatment including methotrexate, cyclosporine, and tacrolimus to help avoid GVHD.[37] The patient completed the BMT and all additional treatment with little to no complications, including no adverse impact on his mental health status. Following his allogeneic BMT procedure, the patient no longer required antipsychotic therapy, had a decrease in his positive and negative symptoms scale (Positive and Negative Symptom Scale - PANSS) score, and an increase in his score on the overall functioning scale (Global Assessment of Functioning Scale - GAF).[38] Even eight years post-BMT, he still showed a resolution of symptoms with no mental health medication or intensive treatment required.[37] Figure 1.1 summarizes his psychiatric disposition both prior and following his BMT procedure.

Table 1. 4 Treatment from Case Report for 24-year-old Schizophrenic Patient Who Underwent BMT[37]

	Before BMT	After BMT	Interpretation	
Medications taken	Quetiapine 800mg/day Risperidone 12mg/day Olanzapine 20mg/day	None		
PANSS -Total score[16]	From 90-110	Approx. 30	Lowest: 24 (No symptoms present)	Highest: 168 (Extremely severe symptoms)
GAF - Total score[17]	Down to 20	Approx. up to 95	Lowest: 1 (Considered suicidal and/or homicidal)	Highest: 100 (Function in a positive manner in their daily life)
Primary symptoms	Hallucinations Delusions	None		

There is also a case report of a patient experiencing the induction of psychiatric symptoms following BMT. A letter to the editor of *Bone Marrow Transplant* describes the case of a 67-year-old patient with no prior history of psychiatric illness who received a BMT for the treatment of with chronic lymphocytic leukemia (CLL) and bone marrow aplasia, requiring weekly blood transfusions.[39] He received bone marrow donated by his brother, who was clinically diagnosed with schizophrenia. Following the transplant, the patient began to complain of frequent hallucinations, bizarre delusions and thought broadcasting with clear consciousness. Although he had complete hematologic recovery, he was unable to be successfully treated for his recent onset psychiatric condition. Risperidone, citalopram, and haloperidol were all administered without success, leading the family to provide comfort care for the patient, who was then lost to follow-up.[40] The

patient later died due to unknown causes. The primary theory that was considered in this report was that of the adoptive transfer of schizophrenia from the brother. While anecdotal, these cases provide evidence of a potential link between schizophrenia and immunity.

GWAS and Potential Mechanistic Explanations

Over the past decade, researchers have begun to examine genomic data in order to evaluate the impact of common genetic variations on human health.[41] The process of genome-wide associated study (GWAS) utilizes experimental genomic databases that allow investigators to study the associations between single-nucleotide polymorphisms (SNPs) and characteristics of disease.[42] The prevalence of SNPs are compared between subjects with a history of a diagnosis versus a control population to determine whether an association exists.[43]

Genes are the small hereditary components that make each human unique by comprising the chromosome. Genes are made of deoxyribonucleic acid (DNA) and provide both structural (genotypic) and physical (phenotypic) characteristics.[44] On each chromosome, there are specific locations referred to as locus (or loci) that contain the one or more specific genes.[45] These loci are utilized as markers of specific locations, especially when certain genetic mutations are being studied and attempted to be located through genome mapping.[45]

There are multiple factors that determine the extent to which a GWAS is successful. These factors include (1) the number of loci affecting the trait in the effected population, (2) the distribution of these loci's allele frequency (called genetic architecture), (3) the sample size, (4) the genome-wide database used in the GWAS and (5) how heterogeneous the trait and/or disease is.[46] This provides context for how to evaluate these studies, which is critical because there are extremely specific evaluations that differ from one study to the next.

GWAS initially evaluated the genomic characterization of common conditions including type-2 diabetes and autoimmunity, but slowly has increased to include psychiatric conditions. The psychiatric data has now been refined into a secondary database called the Psychiatric Genomics Consortium (PGC).[47] There are over 900

investigators from 40 countries that have contributed to the PGC network which includes more than 400,000 human participants.[48] The mental health disorders included in this database are anxiety disorders, major depressive disorder (MDD), manic depressive disorder (bipolar), schizophrenia, suicide attempts, and substance use disorders. Investigators are currently expanding the PGC to also include anorexia nervosa (AN), autism, OCD/Tourette's syndrome and PTSD.[48]

The primary psychiatric diagnosis that has been reviewed through GWASs is schizophrenia. Schizophrenia is noted to have a high heritability of approximately 64-81%.[47] In 2009, this was first reviewed to find 3,000 cases linked to a specific genomic locus that then grew to include over 35,000 cases in 2014.[43] This study also found 108 risk loci associated with schizophrenia that affects enhancers in the brain and immune tissues.[49] More specifically, these SNPs linked with schizophrenia were also associated with glutamatergic transmission, calcium channels and potential changes in immunomodulation.[43] These results continue to support the likelihood that immune function plays a specific role on psychiatric conditions, especially those affected by cognitive function impairment—autism spectrum disorder, Alzheimer's disease, and/or schizophrenia.

A secondary study has identified additional gene SNPs that are enriched in patients diagnosed with schizophrenia. A case found a cross-phenotypic link between schizophrenia and different metabolic processes. The SNP primarily involved was rs13107325-T and the metabolic processes included were body mass index (BMI), high density lipoprotein (HDL) cholesterol, blood pressure and N-terminal pro b-type natriuretic peptide in the acute coronary syndrome.[49] These findings introduced the idea that not only could schizophrenia and/or other mental health conditions may be associated with immune function changes, but potentially metabolic function could also be associated with mental health conditions. In addition to this specific SNP associated with metabolic processes and schizophrenia, patients with this SNP also had an increased likelihood to have cardiovascular disease, lung cancer and bipolar disorder, meaning that this specific SNP could be associated with a wide variety of conditions that scientists would have not previously associated with one another, although the association between schizophrenia and bipolar disorder were not statistically significant.

There are no specific genes that have been associated with being diagnosed with a specific psychiatric condition, but more SNPs are being identified each day that may play a role in how patients develop symptoms. The process of identifying mutations and genetic components associated with psychiatric conditions will continue to evolve over time, but it does provide a potential framework for future research to study more specific genes (like *Hoxb8*). These GWASs could lead to additional treatment options that are more patient specific instead of the iterative model currently being utilized to allow mental health patients to find their optimal therapy. Additionally, these GWASs could also lead to the discovery of new therapeutic targets which could provide better patient-specific therapies.[42]

Summary

These studies define a potential association between psychiatric conditions and an immune-related mechanism that may, in turn, provide a therapeutic target for select patients. The purpose of this thesis is to better understand the potential role of immunity in the pathogenesis of psychiatric conditions. Although multiple theories regarding the mechanisms of immune system influence in mental health pathology to our knowledge medication use before and after BMT has not been studied. This connection has not been previously reviewed using a large-scale population. We hypothesize that there is a measurable relationship between BMT and the induction and/or reversal of psychiatric pathology.

Our study utilized medication use and adherence as a surrogate to measure the severity of psychiatric illness. We chose to utilize medication use, specifically through medication possession ratios (MPR) and proportion of days covered (PDC), because it provided an analysis of patients' treatment over time. The reversal of psychiatric diagnoses in patient medical records is rare, so utilizing medication use provided a method to monitor a patients' symptoms, rather than an objective removal of a diagnosis. By comparing medication use before and after BMT in patient populations with previously diagnosed psychiatric disorders, we were able to generate results that support the scientific premise that an immune component may exist to pathologies that alter mental health.

Section Two: Methods

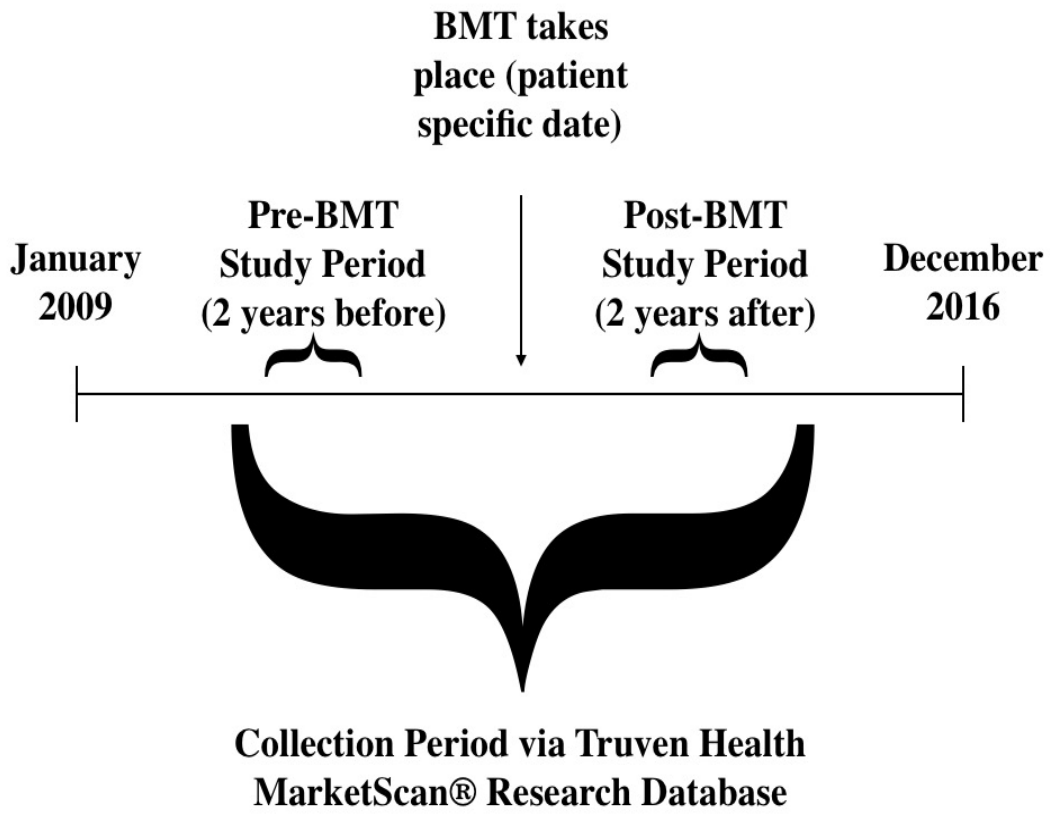
Overview

We conducted a retrospective cohort study that compared the use of psychiatric and pain management medications used in the treatment of psychiatric diagnoses before and after BMT. This study was classified as a quasi-experimental design due to our study population including both those participating as well as others not participating and using an additional medication group for overall comparison. We utilized pre-BMT and post-BMT treatment timeframes and evaluated medications by medication class through generic product identifier (GPI) and Medispan database codes. Medication classes being reviewed include those specific to psychiatric diagnoses and pain management. Antihypertensives were included as a non-psychiatric control class. Antihypertensive medications were determined appropriate for our control because they are a common medication class that manage a lifelong diagnosis with discontinuation of use being rare. As such, two primary analysis groups were identified through generic product identifier (GPI) codes: psychiatric and pain management medication use (exposed) and antihypertensive medication use (unexposed). We used adherence rates, in the form of medication possession ratios (MPR) and proportion of days covered (PDC), to evaluate the utilization changes in each medication group to measure the effects of BMT on a patient's medication management of their primary diagnoses.

Study Population

Enrollees were included in this study if they were 18 years of age or older, had a defined psychiatric disorder, received an allogeneic BMT (both matched sibling and unmatched donors included), and filled outpatient psychiatric or pain management prescriptions within two years before or after the BMT. Conditions studied included bipolar/manic and major depressive disorder, obsessive-compulsive disorder, general anxiety disorder, schizophrenia, suicide attempts, psycho-active substance abuse, opioid-related disorders, post-traumatic stress disorder, panic disorder, alcohol-related disorder, and movement disorders. Diagnostic codes specified by the International Classification of Diseases, versions 9 and 10, are listed in Appendix A.[48,49] Figure 2.1 provides a timeline for data selection.

Figure 2. 1 Timeline for Sample Selection and Eligibility Requirements

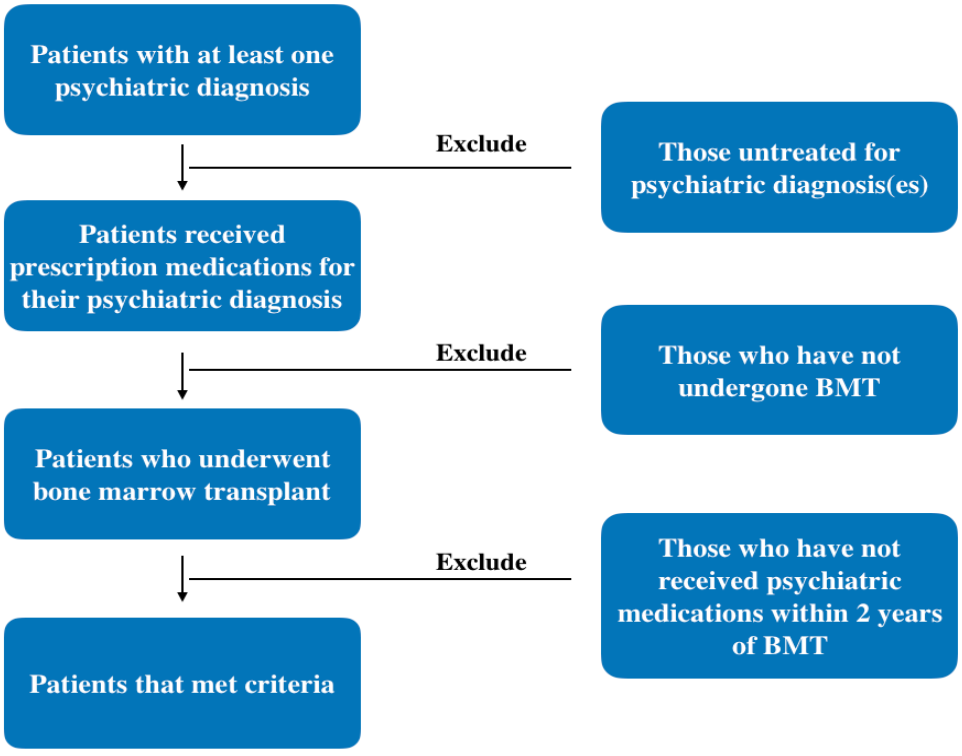


Patients were excluded from this study if they were under the age of 18, if they received an autologous bone marrow transplant, were diagnosed with epileptic disorders through ICD-9 or -10 codes, or if the patient had no final PDC reported following the intervention (due to change in payer or death). Patients that received an autologous BMT were excluded since this procedure involves harvesting the patient's own stem cells and then re-introducing them. Though the immune system is repaired, it still contains the original genetic components, nullifying any potential induction or reversal of a psychiatric condition due to a new immune system. Patients with epilepsy have

medications that overlap with those used to treat manic depression and therefore may skew the results.[50]

Data was gathered from the Truven Health MarketScan® Research Database and included patients enrolled in health plans between January 2009 and December 2016 with medications being reviewed if they were filled within two years before or after the BMT index date.[51] We collected medical and prescription claims through this database from nearly 350 private payers. This database included patients that were de-identified and anonymous. Therefore, the study did not meet the federal definition of human subjects research, exempting it from IRB approval.[52] Additionally, medication identifiers were collected from the Medi-Span® network and utilized GPI codes for group classifications.[53] Appendix B provides specific codes used throughout the study. Figure 2.2 provides a flow diagram of the subject selection process for our patients and the medications reviewed.

Figure 2. 2 Study Population



Exposure and Outcomes

The quasi-experimental design provided a method to analyze and review the utilization rates before and after BMT for our primary association medication classes and a non-related medication class (antihypertensives). Exposed subjects were those that were treated with prescriptions for psychiatric conditions and/or pain management while those unexposed were classified as those with prescriptions for antihypertensive medications. Patients with both exposed and unexposed groups are included in this study since the primary focus was the relationship and analysis between pre- and post-BMT rather than differences between medication classes.

The primary outcome was to compare total PDCs before and after BMT per patient for each medication class. This analysis was completed for each medication group including the exposed and unexposed medication groups. Furthermore, PDC ratios (before/after and after/before) were calculated and graphed for each patient in order to visualize overall trends and pinpoint patients that experienced either a dramatic increase or decrease in PDC values. PDC is the recommended methodology by the Pharmacy Quality Alliance and CMS for estimation of medication adherence for patients using chronic medications.[54]

Secondary outcomes included comparison of total MPRs before and after BMT per patient for each medication class as well as overall MPR and PDCs categorized solely by medication class for summary statistics. MPR was not considered a primary outcome because it does not account for a maximum adherence rate due to it being a summation of days used rather than days covered. We decided to include it as a secondary measurement to show the basis of what led us to utilize PDC. Although overall MPR and PDC per medication class does not provide an accurate assessment of change per patient, it provides a baseline review of medication change regardless of individual patients. This initial analysis provided an understanding to warrant additional research on a per patient level for medication classes before and after BMT.

In order to calculate a total MPR and PDC per patient, we performed a summation of the individual MPRs and PDCs for each patient in each medication class. This summation enabled us to calculate a more accurate total MPR and PDC than taking a

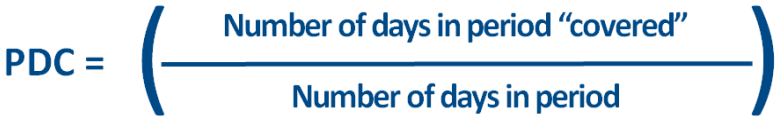
mean value by averaging the individual medication MPRs and PDCs per patient. The total MPRs and PDCs before and after were compared with a paired t-test.

MPR was defined as the total number of days that a medication was dispensed by the pharmacy to each patient, divided by the patient's total follow up time in days, up to two years pre- and post-BMT. Furthermore, this was calculated as the difference between the last and first prescription date plus the supplied days of the last prescription.[55] Although MPR can adequately find baseline information for a patient's medication adherence, it does not have an appropriate maximum, resulting in the ability for adherence to be greater than 100%. This is because MPR includes all similar medications in the numerator, therefore having overlapping medications which may contribute to overestimating the patient's MPR, or adherence.

Due to this limitation, we decided to also find the PDC which accounts for this overestimated adherence concern. Figures 2.3 and 2.4 show the equations for both adherence measurements. PDC was defined as the proportion of days in the measurement period "covered" by prescription claims for the same medication or another in its therapeutic category.[56] The primary difference between each analysis is that PDC only considers days that the patient is covered during a specific time rather than a summation of all days during the medication period. This provided a method to account for multiple medication regimens as well as made it impossible to calculate an adherence greater than 100%.[57]

Figure 2. 3 Equation representing MPR[57]

Figure 2. 4 Equation representing PDC[57]



Confounders

Allogeneic BMT is generally reserved as a secondary treatment options, for hematologic cancers and long-term remission opportunities. For many patients, this means that they are generally more ill than our general population and may have multiple chronic conditions. This can lead to decreased quality of life, increased polypharmacy, and increased medication use. Consequently, the disease burden was determined using the Charlson Comorbidity Index score and individual components that were then reviewed as our primary descriptive characteristics.[58] Of note, subject characteristics including sex, gender, and age, were not identified through Truven's database and are discussed further in the limitations section later in this paper.

An acceptable percentage for adherence in most chronic disease states is generally around 0.8 (80%).[59] Those with major psychiatric diagnoses, however, suffer from debilitating illness and a lack of motivation due to adverse effects and impaired cognitive function, leading to a decreased adherence approximately being 0.5-0.6 (50-60%) with certain conditions, like schizophrenia, having an adherence of approximately 0.35 (35%).[60] Consequently, we considered ≥ 0.5 (50%) to be an adherent patient for our study while those < 0.2 (20%) being considered as having a low adherence (potentially considered a discontinuation of the medication) when assessing their final PDC and MPR values.

Statistical Analysis

Descriptive statistics were determined for patient comorbidities using the Charlson Comorbidities Index and frequencies were assessed for these conditions among the population. Summary statistics were calculated for each medication class. The

difference in overall number of prescriptions was examined. Additionally, the mean MPRs and PDCs before and after BMT per medication class were also determined and included in summary statistics.

Analysis of the total PDCs and MPRs per patient for each medication class before and after BMT was conducted using paired t-tests. Confidence intervals were also reported for MPR and PDC for each medication class per patient. These 95% confidence intervals are defined as the range that the actual mean value lies within 95% confidence and at a statistical significance level of 0.05. Q-Q plots were used to asses normal distribution. Bivariable analyses used non-parametric testing strategies such as the Kruskall-Wallis test to measure the effect of each adherence variable comparing results before and after each patient's BMT. The Dunn test was utilized to account for multiple comparisons for values of statistical significance.

A two-tailed analysis and paired t-tests were completed with statistical significance defined at a p-value < 0.05. All data analysis was completed using SPSS Version 26.0.[61] This study's data represents proprietary information used for research by the Institute for Pharmaceutical Outcomes and Policy at the University of Kentucky College of Pharmacy.

Section Three: Results

Study Population

The study population that was obtained through the Truven Health MarketScan® Research Database and the method used to apply inclusion criteria are depicted in Figure 3.1. The final group for analysis included 8,233 patients who had a psychiatric diagnosis, underwent BMT, and received medication for treatment of a psychiatric condition within 2 years. The number of prescriptions for the treatment of each condition, along with the number of prescriptions for antihypertensives in these patients, are listed below.

Figure 3. 1 Subject Selection Process

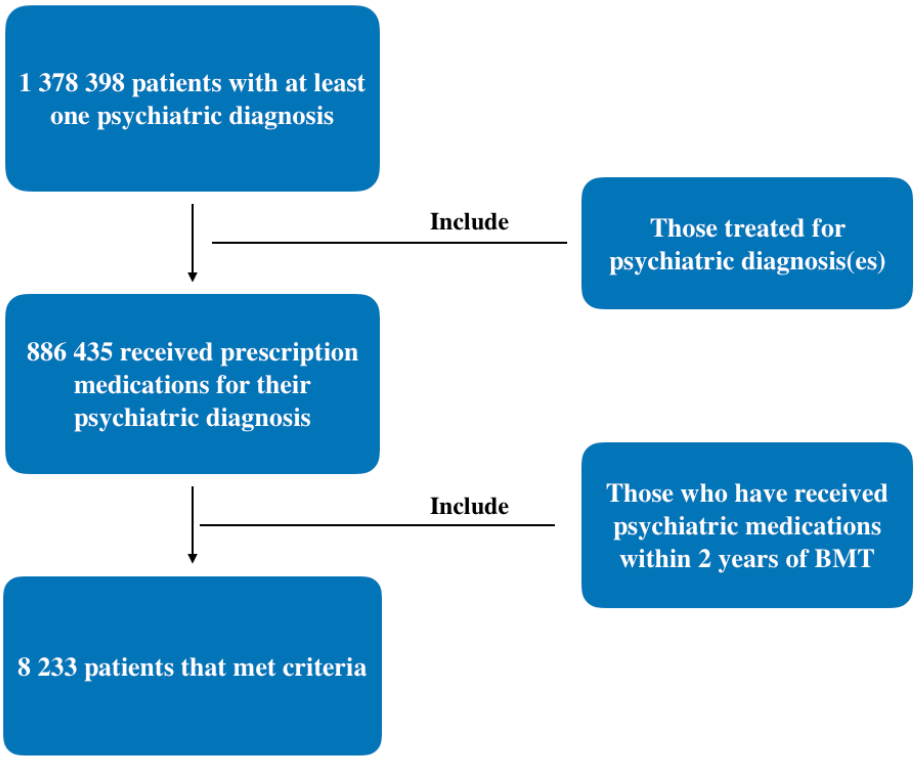
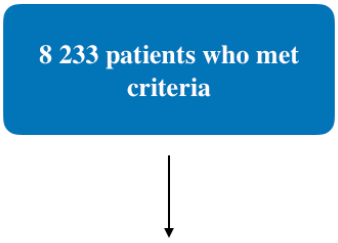


Figure 3.1 Subject Selection Process (Continued)



Medications	Number of Prescriptions
Adhd/Anti-narcolepsy/Anti-obesity	2 111
Antianxiety	6 393
Anti-convulsants	6 697
Antidepressants	28 744
Antipsychotics	4 603
Benzodiazepines	13 303
Hypnotics	8 719
Migraine management	3 319
Opioids	40 208
Antihypertensives (control)	9 308

In addition to the prescriptions patients received, we also assessed the frequency and percentages of comorbidities for our patient population through analysis of Charlson Comorbidity Index in Medispan. These results are listed in Table 3.1. This table reflected what was anticipated to be the most likely comorbidity in the patient population (cancer). It was surprising, however, that more patients than 81.6% did not have a cancer diagnosis since BMT is generally only utilized post-chemotherapy associated with cancer.

Table 3. 1 Comorbidities Frequencies and Percentages

	Frequency	Percent
Cancer	6 718	81.6%
Renal Disease	387	4.7%
Diabetes Type 2	272	3.3%
COPD	206	2.5%
Metastatic Disease	165	2%
Congestive Heart Failure	140	1.7%
Cardiovascular Disease	90	1.1%
Severe Liver Disease	74	0.9%
Diabetes Type 1	41	0.5%
Peripheral Vascular Disease	41	0.5%
Rheumatoid Disease	25	0.3%
Hemiplagia	25	0.3%
Myocardial Infarction	25	0.3%
Severe Liver Disease	8	0.1%
Peptic Ulcer Disease	8	0.1%
AIDS/HIV	8	0.1%
Dementia	8	0.1%

Descriptive Analysis

To determine the effect of BMT on psychiatric medication utilization, medication adherence PDC was used as a primary outcome, with MPR used as a secondary outcome. Both MPR and PDC were included because they each are associated with different limitations.

MPR was calculated by taking the sum of all medication days' supply filled divided by the total days in the period. As discussed in the Methods section, this may skew the results to overestimate the MPR and ultimately, a patient's adherence rate, due to the fact that there is not a maximum number for the ratio when patients receive multiple medications for the treatment of a diagnosis. In order to minimize overestimation, MPRs included in this study were limited to a maximum ratio of 5.[62] PDC, however, eliminates this issue by having a natural maximum of one. PDC measures the portion of days covered in a given time period by at least 1 medication to treat that

diagnosis rather than a total days supplied of all medications that may have overlapped for that same period.

The changes in total before and after prescription count per medication class were calculated for the data sets. The number of prescriptions received by patients, grouped by medication class, are presented in Table 3.2 (MPR) and Table 3.3 (PDC).

Table 3. 2 Number of Prescriptions Prior and Following BMT Used for MPR Calculations

MPR Prescriptions	Before BMT	After BMT	Percent Change
ADHD	606	357	-41.1%
Anti-anxiety	1944	1451	-25.4%
Anticonvulsants	1995	1792	-10.2%
Antidepressants	7093	5538	-21.9%
Antipsychotics	1195	895	-25.1%
Benzodiazepines	4046	2666	-34.1%
Hypnotics/Sedatives	2440	1481	-39.3%
Migraine Medications	1004	859	-14.4%
Opioids	11885	9591	-19.3%
Control: Antihypertensives	2504	1993	-20.4%

Table 3. 3 Number of Prescriptions Prior and Following BMT Used for PDC Calculations

PDC Prescriptions	Before BMT	After BMT	Percent Change
ADHD	567	327	-42.3%
Anti-anxiety	1752	1367	-22.0%
Anticonvulsants	1755	1657	-5.6%
Antidepressants	6236	5108	-18.1%
Antipsychotics	1071	829	-22.6%
Benzodiazepines	3819	2585	-32.3%
Hypnotics/Sedatives	2271	1417	-37.6%
Migraine Medications	889	807	-9.2%
Opioids	11156	9341	-16.3%
Control: Antihypertensives	2155	1805	-16.2%

This data demonstrates that the total number of prescriptions in each medication class analyzed decreased after BMT in our patient cohort. ADHD medications, benzodiazepines and hypnotics/sedatives had the greatest decreases in overall prescriptions after BMT with mean decreases of 42%, 33% and 38% respectively. Between the two tables, the total prescription count is higher in each medication class for the MPR data since each medication is counted regardless of prescription overlap whereas for PDC overlapping prescriptions count as one.

Univariate and Bivariate Analyses

Table 3.4 depicts the overall change in mean MPRs calculated for each drug class before and after BMTs. This data is graphically represented in Figure 3.2.

Figure 3. 2 Summary Statistics of Pre- and Post-BMT in Mean MPR

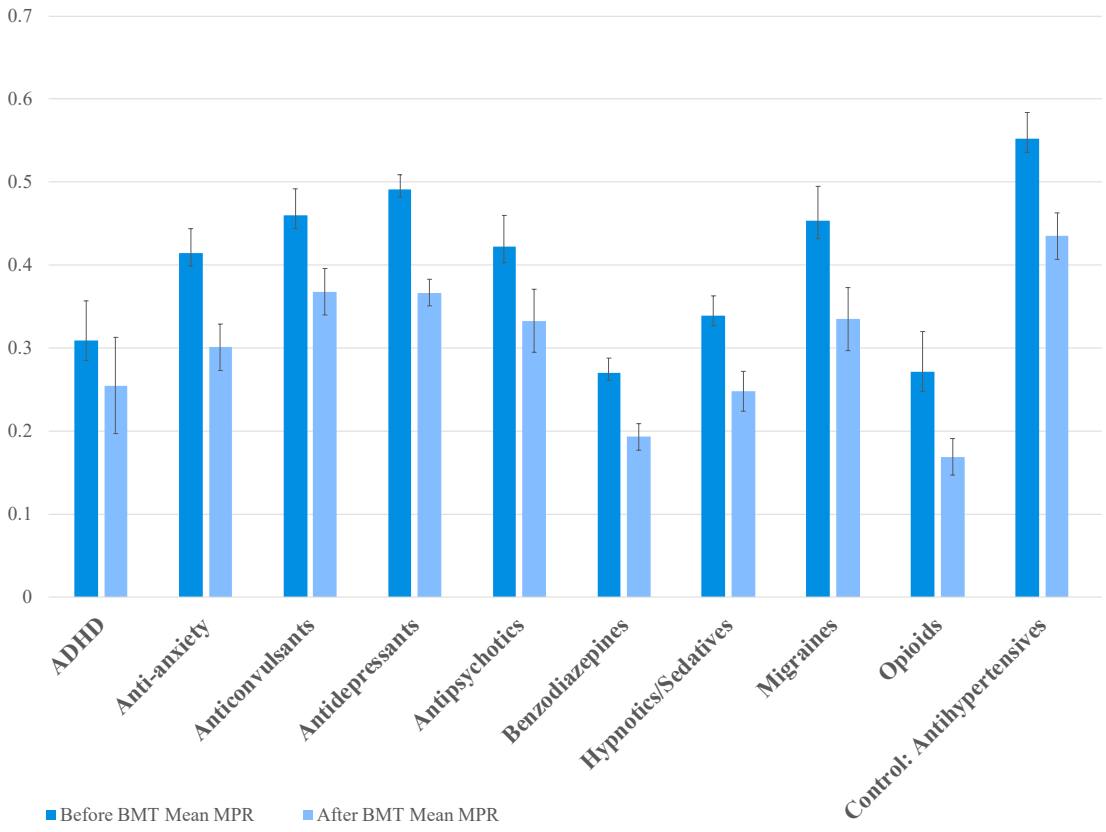


Table 3. 4 Pre- and Post-BMT in Mean MPR

	Mean MPR		Raw Difference	Percent Change
	Before BMT	After BMT		
ADHD	0.309	0.255	0.054	-17.6%
Anti-anxiety	0.414	0.301	0.113	-27.3%
Anticonvulsants	0.460	0.368	0.092	-20.1%
Antidepressants	0.491	0.367	0.124	-25.3%
Antipsychotics	0.422	0.333	0.089	-21.1%
Benzodiazepines	0.270	0.193	0.077	-28.7%
Hypnotics/Sedatives	0.339	0.248	0.092	-27.0%
Migraines	0.453	0.335	0.119	-26.2%
Opioids	0.272	0.169	0.102	-37.6%
Control: Antihypertensives	0.552	0.435	0.117	-21.1%

Overall, the MPR values ranged from 0.17 to 0.55 with antidepressant medications having the largest raw difference, decreasing by 0.124. Opioids had the greatest percent change between pre- and post-BMT MPR at -31.6% with a raw difference of 0.103. Each medication class exhibited an overall decrease in MPR after the BMT compared to pre-BMT values.

MPR was also calculated for each medication class for each individual patient. Table 3.4 identifies trends in the overall medication class while this analysis highlights the changes at the individual patient level. This calculated data included evaluating the change in total MPR before and after BMT. In order to determine the statistical significance of these changes, a paired t-test was conducted since each patient had a before and after value to directly compare. Table 3.5 depict these results. All decreases in

MPR were statistically significant ($p < 0.05$) with all but antipsychotics being highly statistically significant ($p < 0.001$).

Table 3. 5 Bivariate analysis with MPR per patient grouped by medication class as the outcome of interest

		Before BMT		After BMT			95% CI of the Difference	
	N	MPR Sum	SD	MPR Sum	SD	P-value	Lower	Upper
ADHD	49	2.516	2.125	1.075	1.547	0.0001	0.811	2.072
Anti-anxiety	199	2.818	3.022	1.413	2.704	0.0001	0.926	1.883
Anticonvulsants	195	3.319	3.991	1.805	3.298	0.001	0.959	2.068
Antidepressants	618	4.106	3.816	2.080	2.951	0.0001	1.703	2.348
Antipsychotics	77	3.758	3.488	2.452	4.525	0.019	0.216	2.395
Benzodiazepines	420	1.735	2.599	0.834	1.658	0.0001	0.641	1.161
Hypnotics/Sedatives	212	2.409	2.484	0.991	1.869	0.0001	1.063	1.775
Migraines	72	4.371	3.777	1.902	2.610	0.0001	1.514	3.423
Opioids	1204	2.055	2.952	0.975	2.019	0.0001	0.906	1.253
Control: Antihypertensives	229	4.246	3.725	2.469	3.450	0.0001	1.192	2.363

Figure 3.3 and Table 3.6 present mean PDC values pre- and post-BMT grouped by medication class while Table 3.7 contains the pertinent results of bivariate analysis of the PDC data analyzed for individual patients.

Figure 3. 3 Summary Statistics of Pre- and Post-BMT in Mean MPR

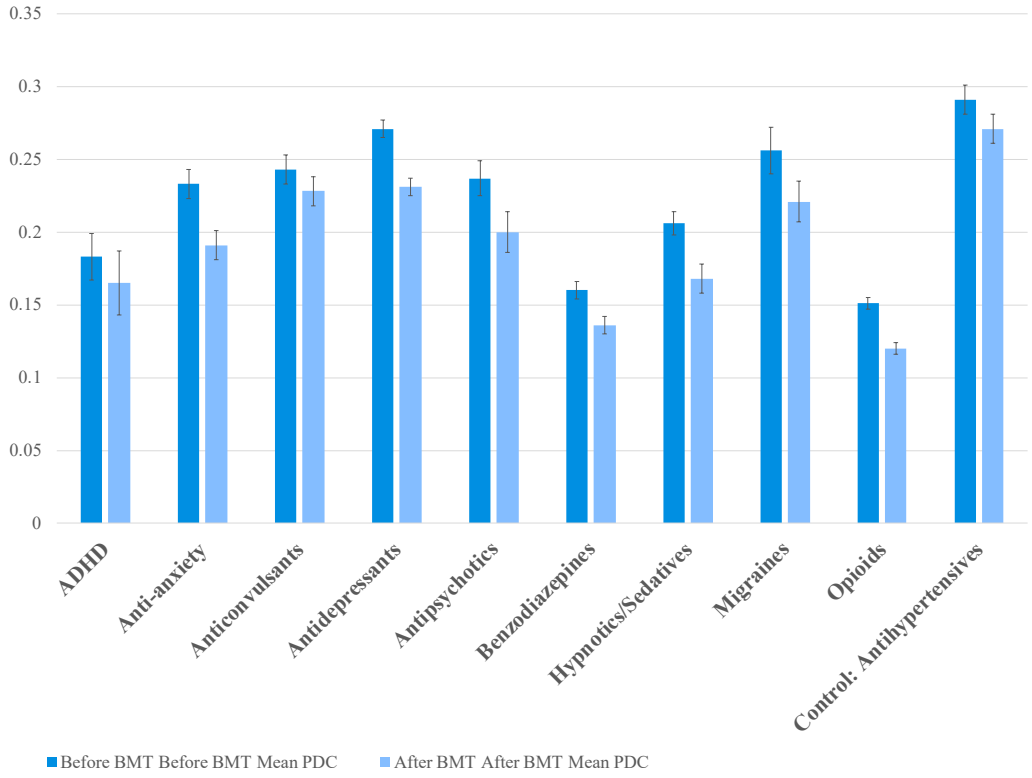


Table 3. 6 Pre- and Post-BMT Mean PDC

	Mean PDC		Raw Difference	Percent Change
	Before BMT	After BMT		
ADHD	0.183	0.165	0.018	-9.8%
Anti-anxiety	0.233	0.191	0.042	-17.9%
Anticonvulsants	0.243	0.228	0.014	-5.9%
Antidepressants	0.271	0.231	0.040	-14.9%
Antipsychotics	0.237	0.200	0.037	-15.7%
Benzodiazepines	0.160	0.136	0.024	-15.1%
Hypnotics/ Sedatives	0.206	0.168	0.038	-18.2%
Migraines	0.256	0.221	0.035	-13.5%
Opioids	0.151	0.120	0.031	-20.4%
Control: Antihypertensives	0.291	0.271	0.021	-7.0%

Overall, the PDC values were approximately 50% lower than the corresponding MPR value resulting in a range from 0.12 to 0.27. Similar to MPR, across each medication class, the PDC values decreased post-BMT with antidepressants again having the largest raw difference. Opioids, however, had the largest percentage decrease. Though the raw PDC values are lower than the corresponding MPR values truncating the raw difference between post- and pre-BMT values, the percent decrease in PDC values mirrors that of the MPR values. Of note, antihypertensive medications had the smallest percent change for both MPRs and PDCs.

The PDC values for each medication class when calculated on a per patient basis are listed in Table 3.7. P values as calculated using paired t tests, along with 95% confidence intervals, are included.

Table 3. 7 Bivariate analysis with PDC per patient grouped by medication class as the outcome of interest

		Before BMT		After BMT			95% CI of the Difference	
	N	PDC Sum	SD	PDC Sum	SD	P-value	Lower	Upper
ADHD	52	1.418	0.962	0.726	0.797	0.0001	0.345	1.039
Anti-anxiety	181	1.402	1.441	0.865	1.241	0.0001	0.320	0.753
Anticonvulsants	174	1.409	1.760	1.180	1.849	0.078	-0.026	0.485
Antidepressants	563	1.910	1.706	1.325	1.564	0.0001	0.427	0.745
Antipsychotics	70	1.519	1.489	1.290	1.389	0.26	-0.173	0.631
Benzodiazepines	405	0.902	1.190	0.573	0.982	0.0001	0.204	0.454
Hypnotics/Sedatives	198	1.260	1.356	0.696	1.051	0.0001	0.362	0.765
Migraines	66	2.031	1.981	1.478	1.718	0.066	-0.039	1.145
Opioids	1154	1.059	1.335	0.666	1.106	0.0001	0.317	0.470
Control: Antihypertensives	203	1.831	1.534	1.485	1.646	0.012	0.076	0.616

Results for PDC per patient paralleled those from PDC of overall medication class. The differences were that overall fewer prescriptions were analyzed for the per patient group and the overall decreases were more dramatic.

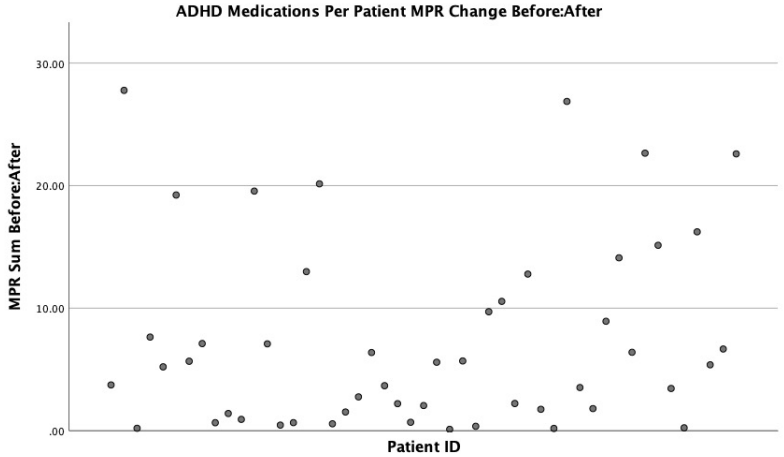
Overall, the results presented show that MPR values provide slightly higher adherence rates as compared to PDC values for medication class. This is due to the number of prescriptions included as well as the ratio having a maximum of 5 (500%) for MPR as compared to PDC's maximum being 1 (100%). Although there is a difference in the adherence overall, both groups showed a reduction in prescriptions and adherence for each medication class. These results were all statistically significant except for anticonvulsant medications reviewed with PDC.

Event analysis for Future Studies

Figures 3.4 through 3.43 provide a visualization for the change in medication utilization for each patient before and after BMT. These scatter plots depict the spectrum of adherence and highlights potential outliers that may be of interest for future prospective and randomized controlled trials. To create these plots, the ratio of post-BMT and pre-BMT PDC or MPR for each patient were plotted on a linear scale. These plots were included to be able to highlight the spectrum of change amongst the patients in order to reveal potential outliers. The before/after plots highlight those patients that experienced an above average decrease in MPR or PDC, while the after/before plots highlight patients with an above average increase in MPR and PDC. These plots provide evidence that there are individual patients that experienced dramatic increased or decreased need for a specific class of medication.

Figures 3.4 through 3.23 depict MPR change comparing patients with a decrease in medication use after compared to before BMT (Before:After) and those with an increase in medication use after compared to before BMT (After:Before). Table 3.8 shows those with the largest decrease or increase (greater than 5) for MPR.

Figure 3. 4 and Figure 3. 5 Scatter Plot of Pre-and Post-BMT MPR Sums per Patient for ADHD MedicationsFigure 3. 6 and



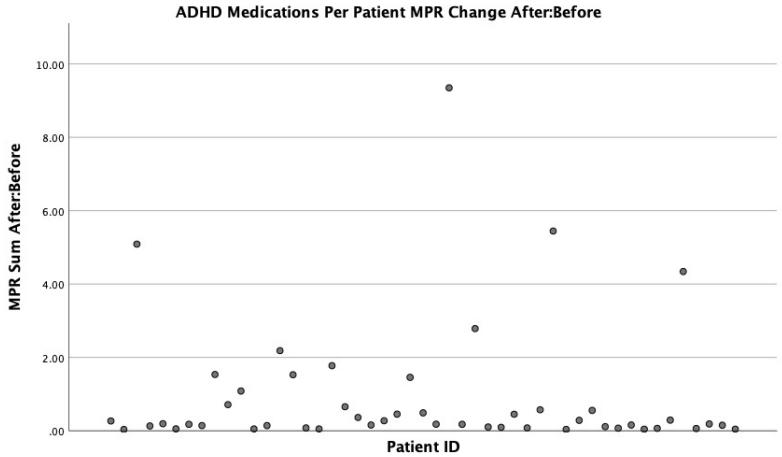
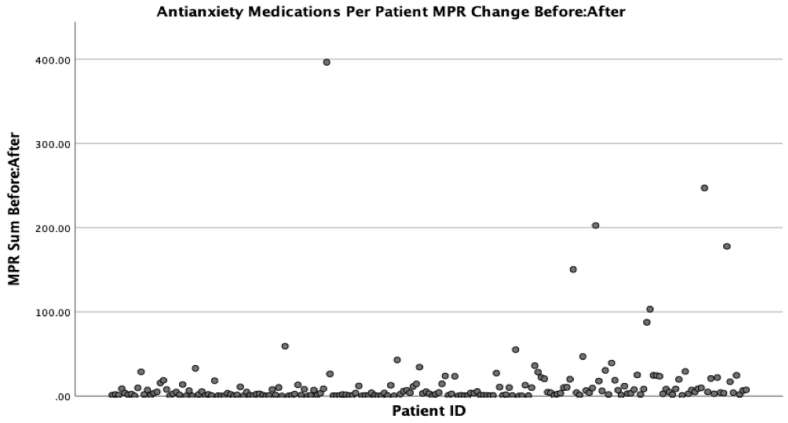


Figure 3. 7 Scatter Plot of Pre-and Post-BMT MPR Sums per Patient for Anti-anxiety Medications



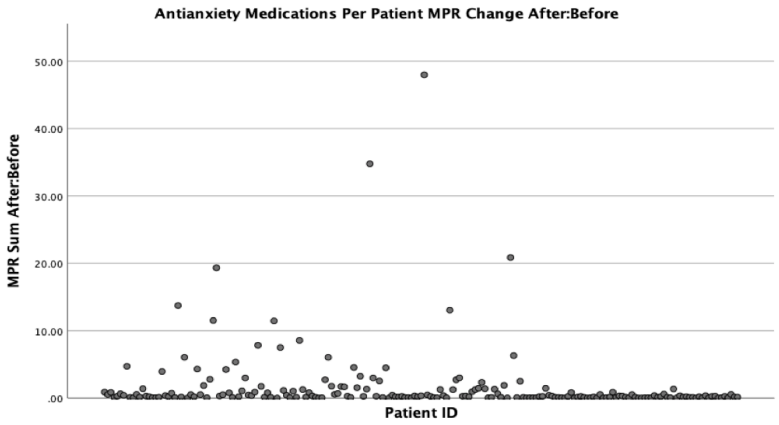
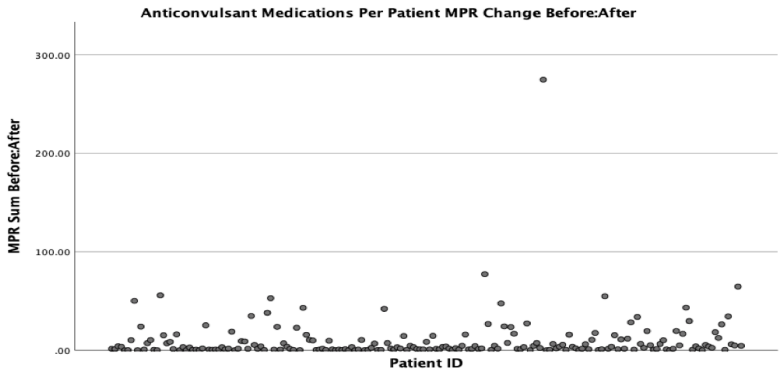


Figure 3. 8 and Figure 3. 9 Scatter Plot of Pre-and Post-BMT MPR Sums per Patient for Anticonvulsant Medications



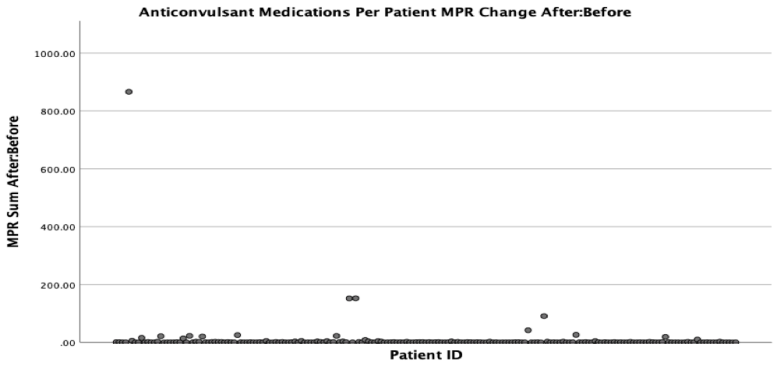
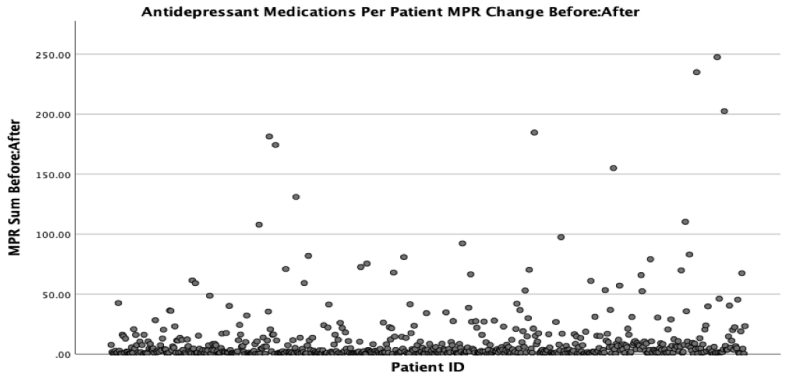


Figure 3. 10 and Figure 3. 11 Scatter Plot of Pre-and Post-BMT MPR Sums per Patient for Antidepressant Medications



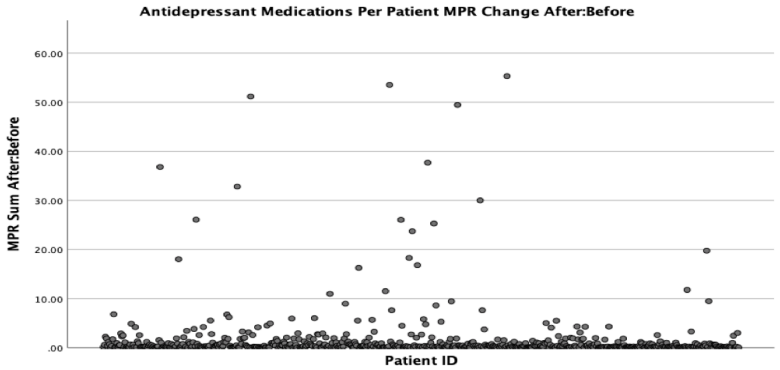
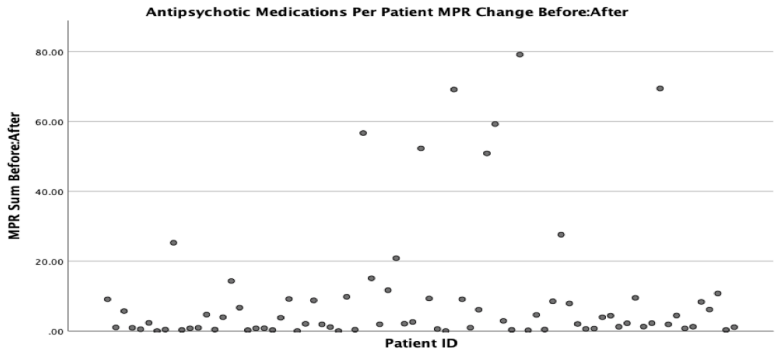


Figure 3. 12 and Figure 3. 13 Scatter Plot of Pre-and Post-BMT MPR Sums per Patient for Antipsychotic Medications



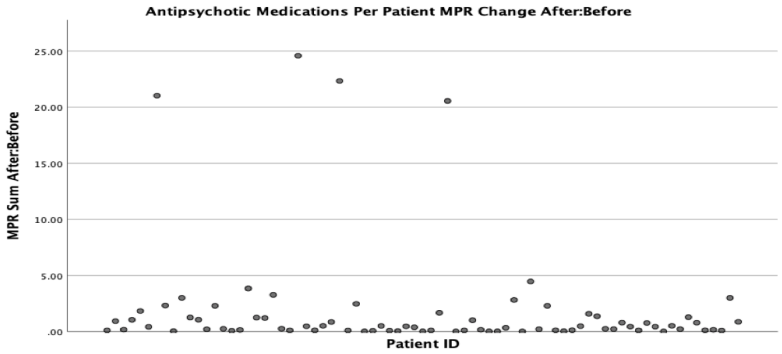
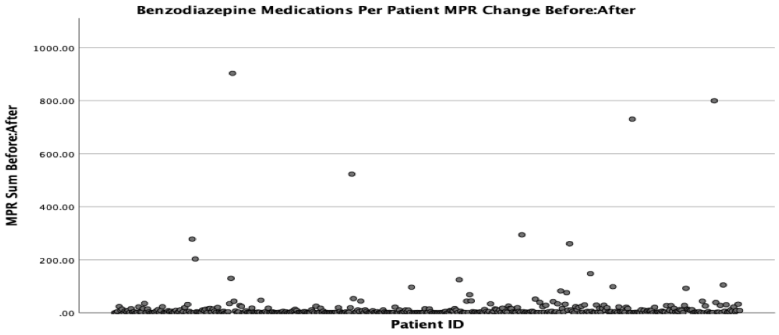


Figure 3. 14 and Figure 3. 15 Scatter Plot of Pre-and Post-BMT MPR Sums per Patient for Benzodiazepine Medications



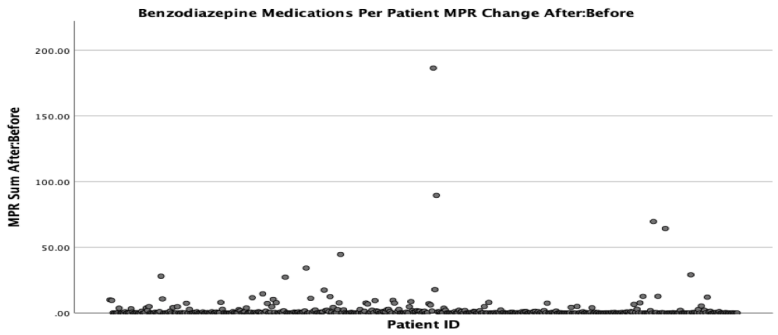
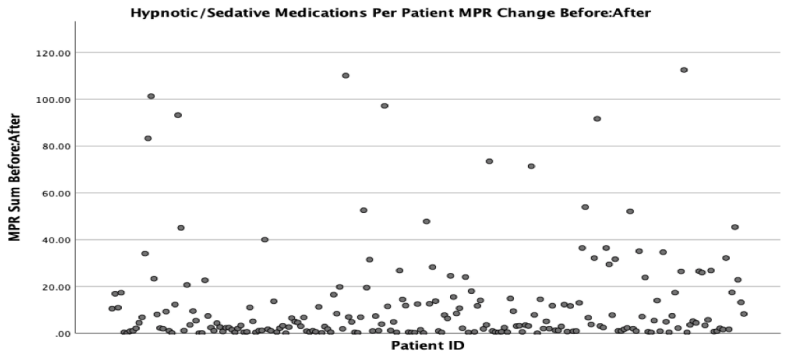


Figure 3. 16 and Figure 3. 17 Scatter Plot of Pre-and Post-BMT MPR Sums per Patient for Hypnotic/Sedative Medications



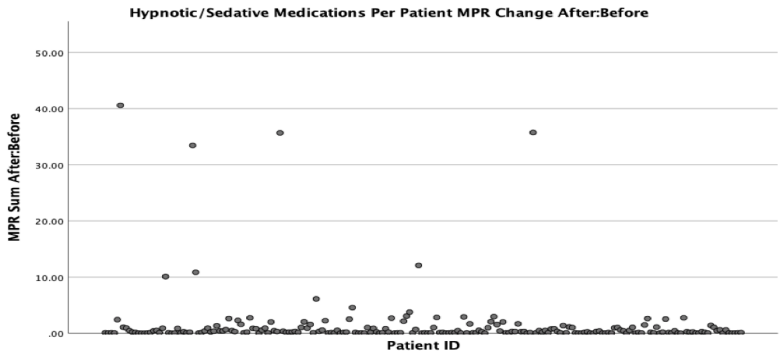
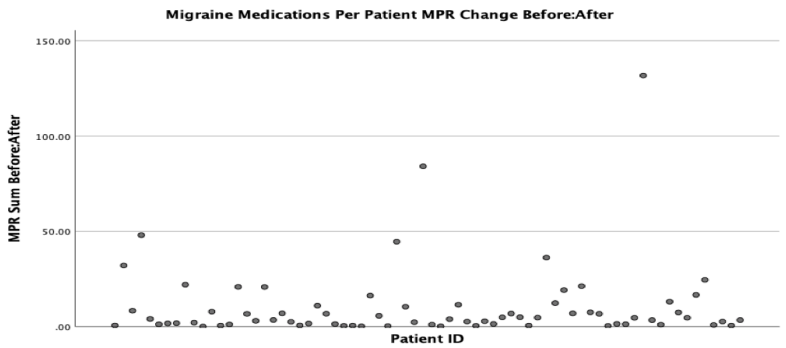


Figure 3. 18 and Figure 3. 19 Scatter Plot of Pre-and Post-BMT MPR Sums per Patient for Migraine Medications



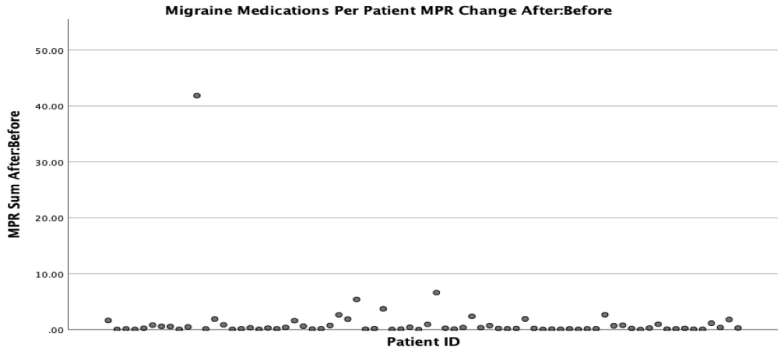
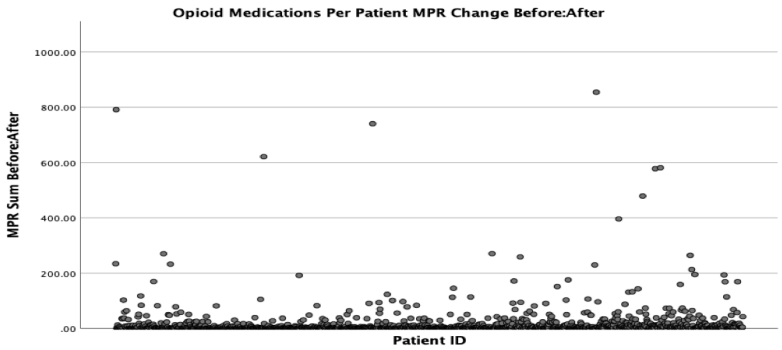


Figure 3. 20 and Figure 3. 21 Scatter Plot of Pre-and Post-BMT MPR Sums per Patient for Opioid Medications



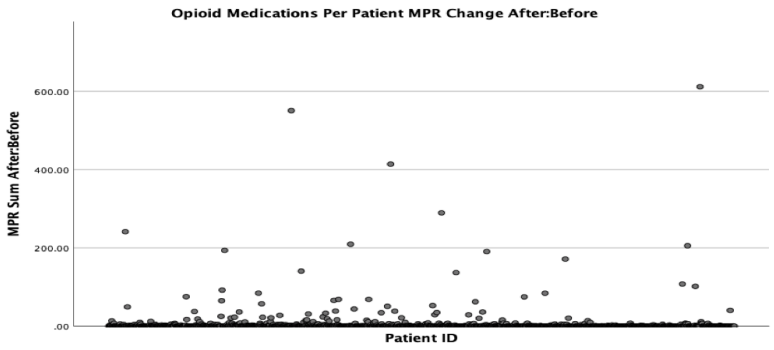
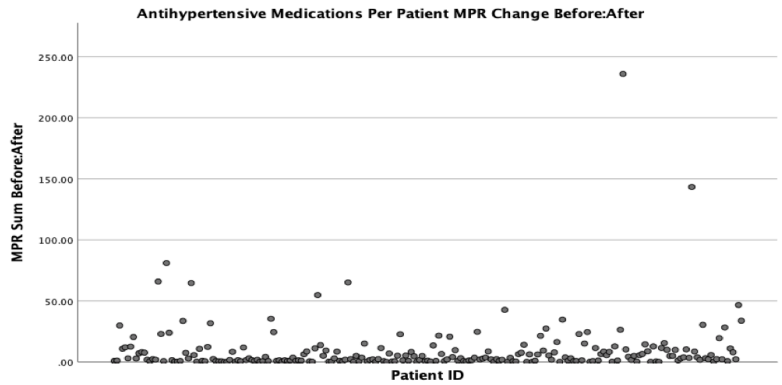


Figure 3. 22 and Figure 3. 23 Scatter Plot of Pre-and Post-BMT MPR Sums per Patient for Antihypertensive Medications



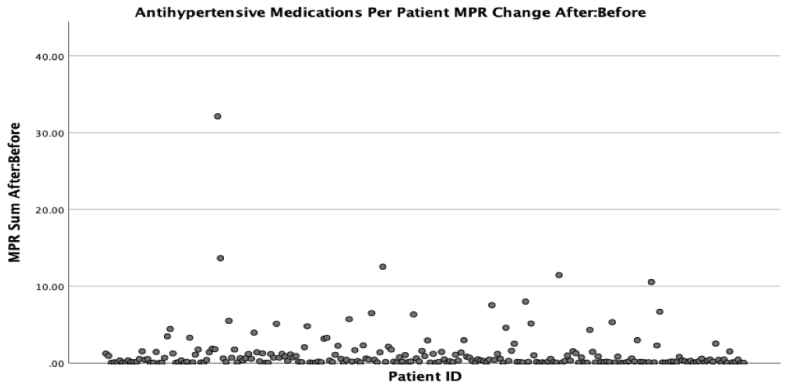


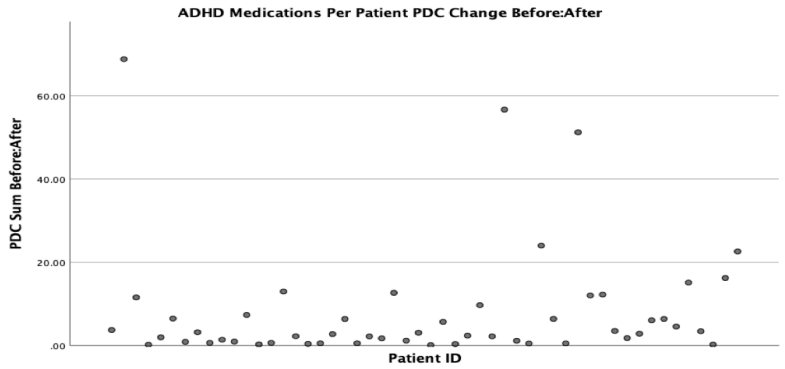
Table 3. 8 Percentages of the Change of PDC Sums with Ratio Greater Than 5

Medication Class	Before:After	After:Before
ADHD	53.1%	6.1%
Anti-anxiety	42.2%	7.5%
Anticonvulsants	36.9%	9.2%
Antidepressants	38.8%	6.1%
Antipsychotics	36.4%	5.2%
Benzodiazepines	40.2%	9.8%
Hypnotics/Sedatives	46.7%	3.8%
Migraine Medications	41.7%	4.2%
Opioids	40.7%	10.3%
Control: Antihypertensives	40.2%	6.6%

Each scatterplot assessed the sum difference of MPR per patient organized by medication class. All medication classes contained outliers with ratios greater than 5 with those having a decrease after BMT (Before:After) having more outliers with a larger range of differences. This provides a visual depiction of specific outliers that could reflect potential change in psychiatric diagnoses due to a complete decrease in medication use.

Figures 3.24 through 3.43 depict PDC change comparing patients with a decrease in medication use after compared to before BMT (Before:After) and those with an increase in medication use after compared to before BMT (After:Before). Table 3.8 lists the percentages of each patients group with a decrease or increase (greater than 5) for PDC.

Figure 3. 24 and Figure 3. 25 Scatter Plot of Pre-and Post-BMT PDC Sums per Patient for ADHD Medications



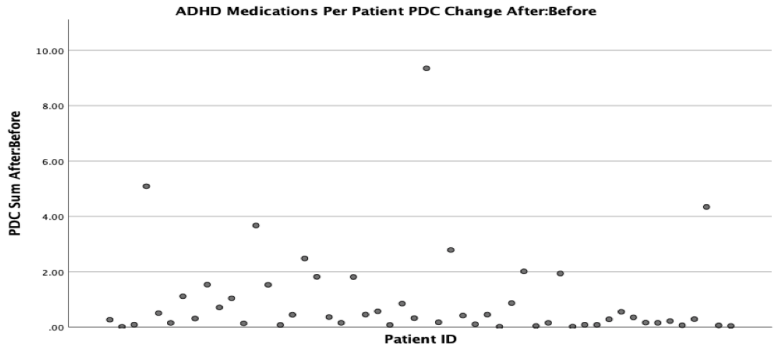
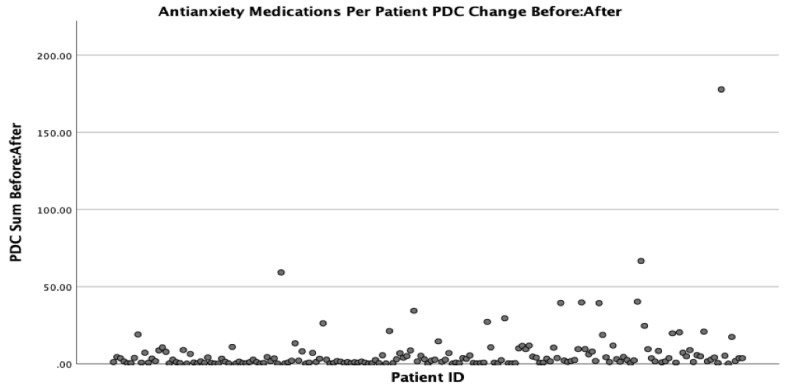


Figure 3. 26 and Figure 3. 27 Scatter Plot of Pre- and Post-BMT PDC Sums per Patient for Anti-anxiety Medications



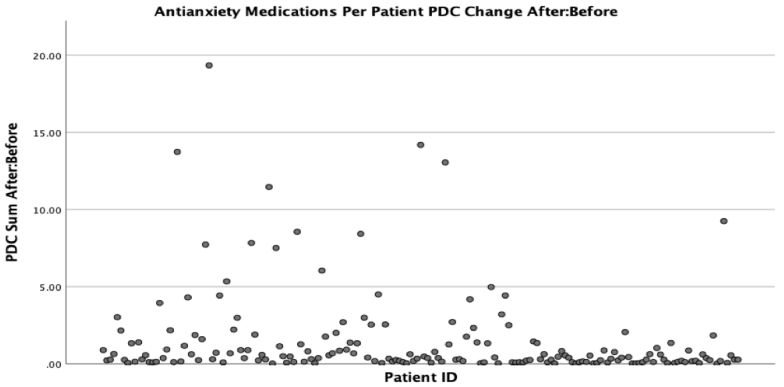
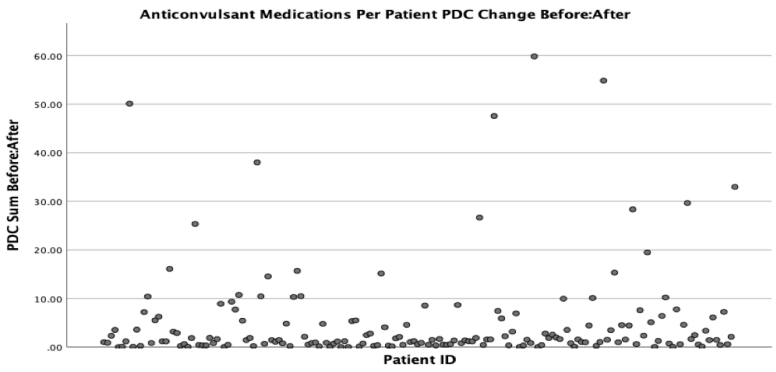


Figure 3. 28 and Figure 3. 29 Scatter Plot of Pre-and Post-BMT PDC Sums per Patient for Anticonvulsant Medications



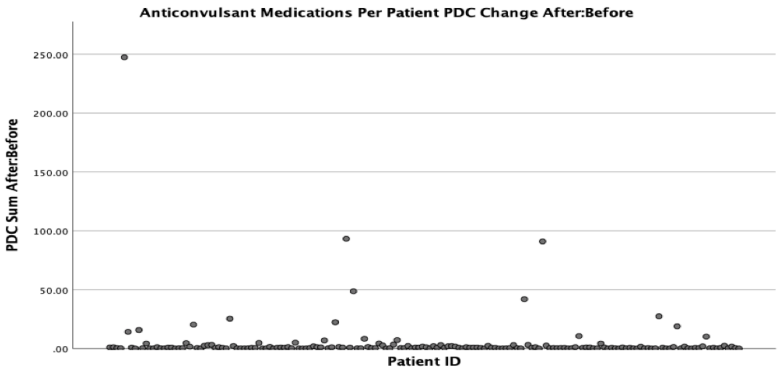
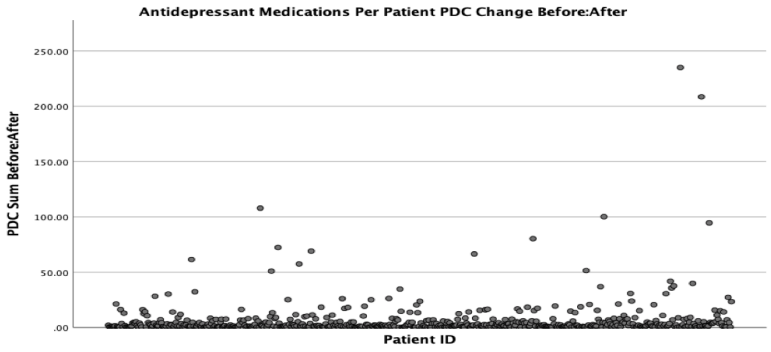


Figure 3. 30 and Figure 3. 31 Scatter Plot of Pre-and Post-BMT PDC Sums per Patient for Antidepressant Medications



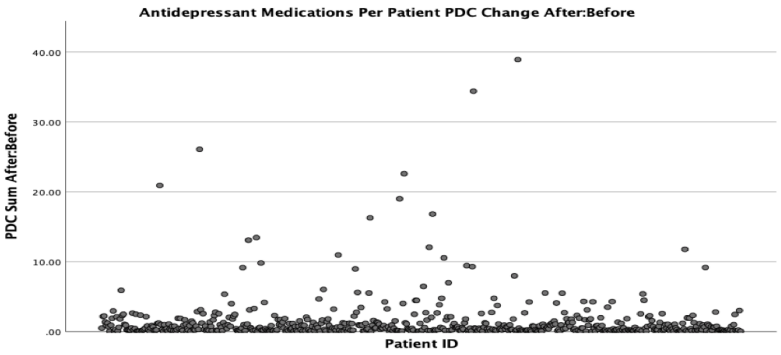
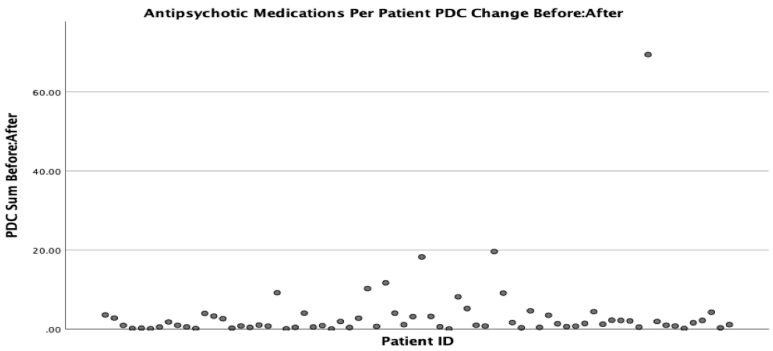


Figure 3. 32 and Figure 3. 33 Scatter Plot of Pre-and Post-BMT PDC Sums per Patient for Antipsychotic Medications



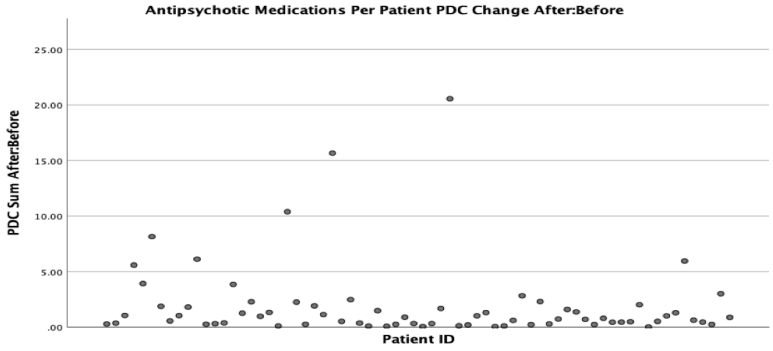
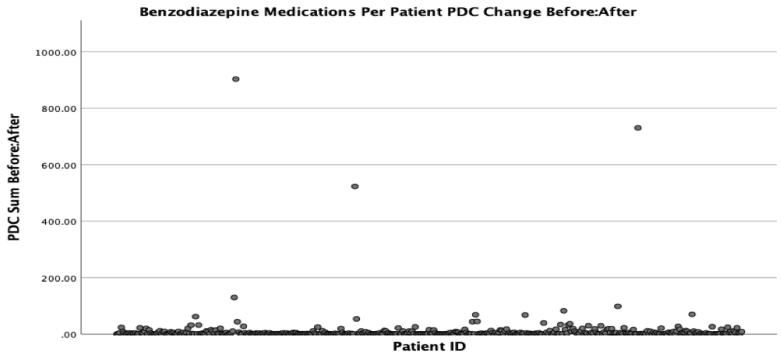


Figure 3. 34 and Figure 3. 35 Scatter Plot of Pre-and Post-BMT PDC Sums per Patient for Benzodiazepine Medications



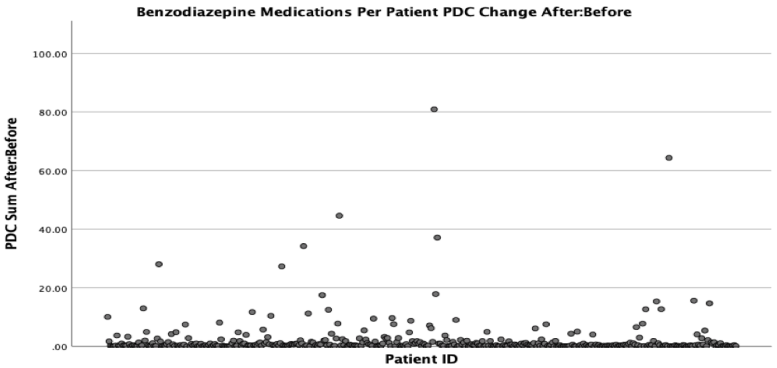
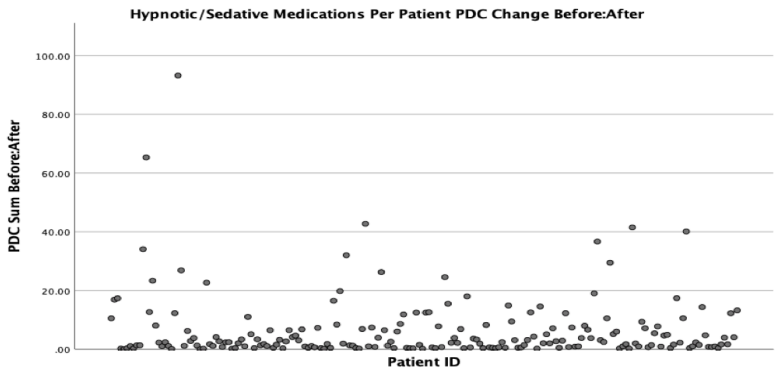


Figure 3. 36 and Figure 3. 37 Scatter Plot of Pre-and Post-BMT PDC Sums per Patient for Hypnotic/Sedative Medications



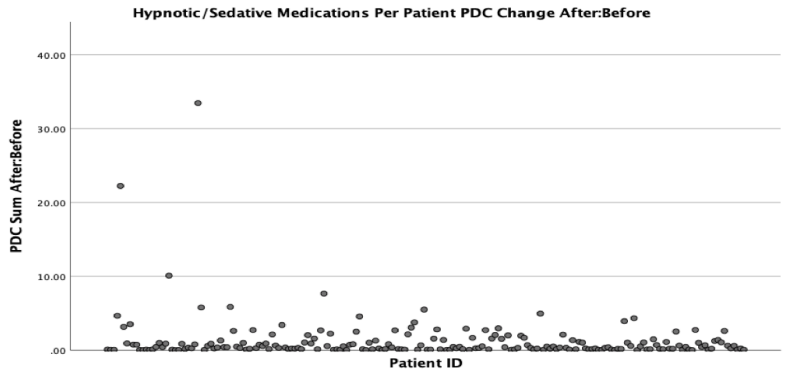
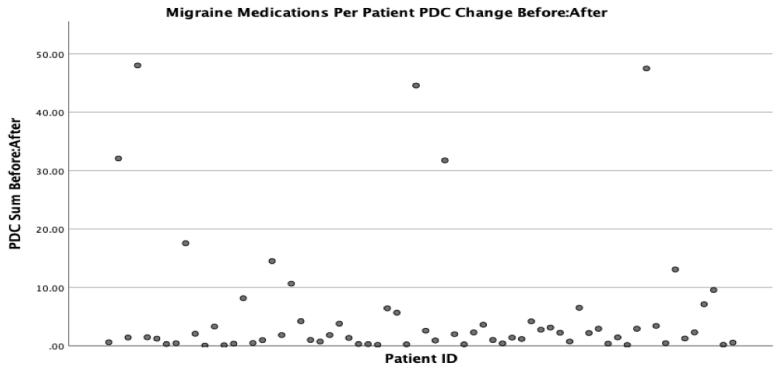


Figure 3. 38 and Figure 3. 39 Scatter Plot of Pre-and Post-BMT PDC Sums per Patient for Migraine Medications



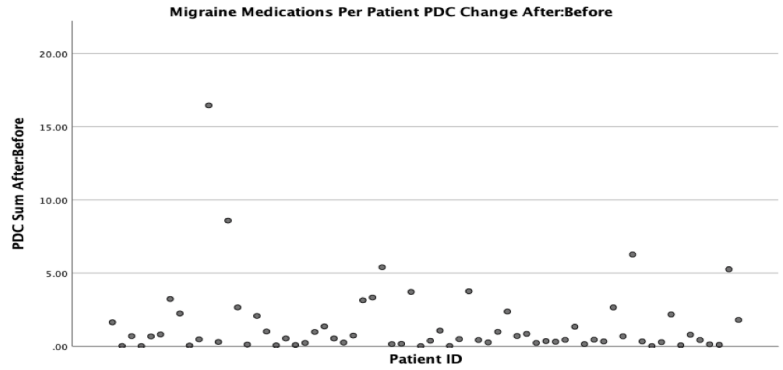
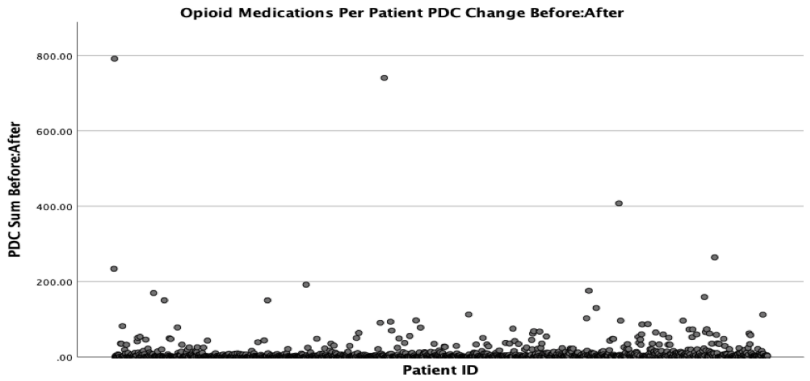


Figure 3. 40 and Figure 3. 41 Scatter Plot of Pre-and Post-BMT PDC Sums per Patient for Opioid Medications



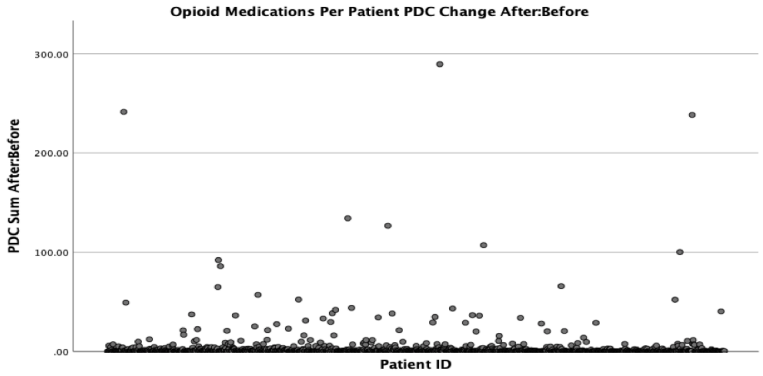
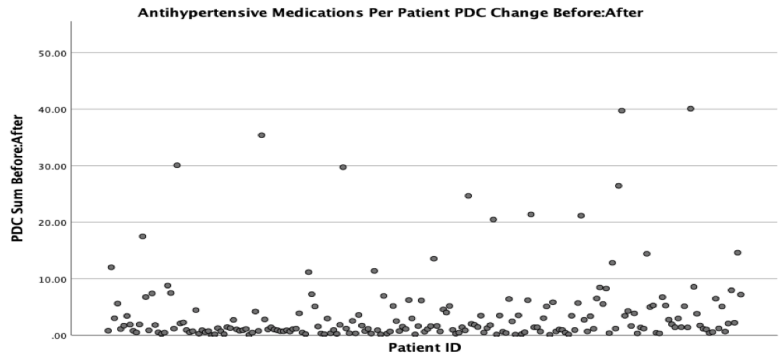


Figure 3. 42 and Figure 3. 43 Scatter Plot of Pre-and Post-BMT PDC Sums per Patient for Antihypertensive Medications



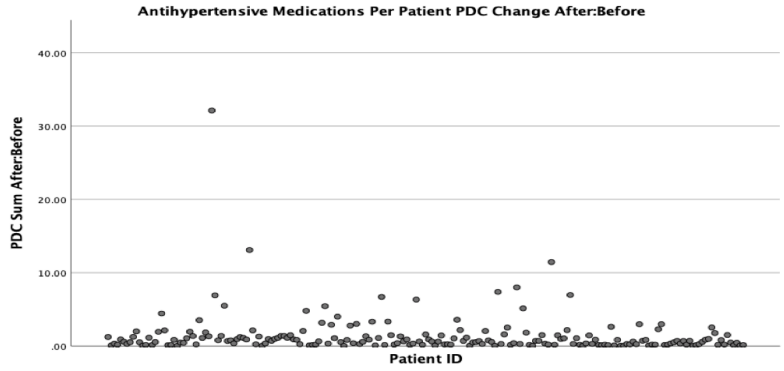


Table 3. 9 Percentages of the Change of PDC Sums with Ration Greater Than 5

Medication Class	Before:After	After:Before
ADHD	38.5%	3.8%
Anti-anxiety	29.8%	7.2%
Anticonvulsants	25.3%	10.3%
Antidepressants	25.6%	5.5%
Antipsychotics	12.9%	10%
Benzodiazepines	31.9%	9.4%
Hypnotics/Sedatives	33.8%	3.5%
Migraine Medications	22.7%	7.6%
Opioids	31.8%	10.3%
Control: Antihypertensives	23.6%	5.9%

Each scatterplot assessed the sum difference of PDC per patient organized by medication class. All medication classes contained outliers with ratios greater than 5 with those having a decrease after BMT (Before:After) having more outliers with a larger range of differences. This provides a visual depiction of specific outliers that could reflect potential change in psychiatric diagnoses due to a complete decrease in medication use.

Section Four: Discussion

Overview

This study is the first to analyze changes in psychiatric condition severity after patients undergo BMT. Medication adherence and the amount of medication needed were utilized to examine this potential relationship. Decreases in patient medication requirements after a BMT procedure may signify a resolution of psychiatric symptoms associated with a given diagnosis. Our results provide evidence suggesting that a reversal of psychiatric pathology occurs in some patients as a result of alteration of their immune system through BMT. This study provides novel insights concerning the potential impact BMT has on patients with psychiatric conditions while also providing evidence that supports the scientific premise encouraging further research in order to solidify the connection between immunologic mechanisms and long-term patient progression.

Event Analysis

Overall, the descriptive statistics show a consistency in the reduction in the number of prescriptions required after BMT compared to before the procedure. Though this decrease does not explicitly reflect any change in patients' psychiatric diagnoses, it does provide evidence that BMT has a general effect of lowering the overall number of prescriptions a patient requires—an indication of a potential reduction or resolution of psychiatric symptoms or comorbidities. The comorbidity frequencies reflect the expected distribution for our patient population. The majority of the patients included in the analysis had a recorded diagnosis of cancer, which is the primary indication for BMT. These comorbidity statistics reflect that the patient population analyzed is a valid sample to investigate the impact of BMT. For comparative note, there is no specific Charlson code for hypertension—the indication for our reference drug class. Therefore, there was no way to determine the frequency of hypertension diagnosis in our study population. The frequency of prescriptions of antihypertensives, however, was similar to expected estimates produced by general prevalence statistics.

Although the number of prescriptions were more numerous than initially anticipated, it decreased significantly when they were matched and examined at the individual patient level. This decrease in prescription count could be the result of frequent

hospitalizations that are not accounted for in the Truven database. This issue is discussed further in the limitations section below.

As for overall MPR and PDC, we were able to document decreases in both values for each medication class, prompting our individual patient analyses. Of note, due to MPR having an overlap in medication use and not accounting for patients filling prescriptions close to their index date, the MPR analysis and data is still inflated due to a maximum possible ratio up to 5 (500% adherence). Though the raw numbers are more inflated, the before and after differences in MPR provide insight into the overall trends in the medication classes. MPR per patient categorized by medication class characterized a major decrease in use from before to after BMT. The MPR data revealed a statistically significant decrease in utilization for all medications, including our control group of antihypertensives showing a potential that cardiovascular conditions may also have a decrease in medication utilization following BMT.

PDC per patient was our primary endpoint. Overall, all medication classes had both a statistically significant decrease in mean PDC and in the total number of prescriptions after BMT, except for anticonvulsant, antipsychotics and migraine medications. When drawing conclusions from this data, statistical versus clinical significance must be considered when comparing each medication class due to our large sample size. Some considerations for future subgroup analyses include studies focusing on specific locations to be able to analyze a smaller patient population to better assess the clinical impact.

This study found that all medication classes examined had reduced use after BMT compared to before the procedure. Even medication classes with small decreases in use were noted to be statistically significant, and therefore these differences may not reflect clinical significance. Due to the large number of prescriptions and patients analyzed, even small decreases in utilization and adherence were highly statistically significant. In order to determine clinical significance, more detailed analysis of individual patients that had extreme changes in medication use, as reflected in the upper regions of the respective scatter plots, could be performed. Through further review, statistical versus clinical significance should be considered, as investigation of additional confounders could be accounted for in order to produce a more accurate assessment and improve our ability to

gauge the clinical significance of the results.

Secondary analyses included in the study were the MPR per patient and PDC per patient scatter plots that measured the difference ratio of after to before medication use for each patient. These plots were included to highlight the spectrum of change amongst the patients in order to reveal potential outliers. The before/after plots highlight those patients that experienced major decreases in MPR or PDC while the after/before plots highlight patients with major increase in MPR or PDC. These plots demonstrate that there were individual patients that had dramatic decrease or increase in medication requirements for specific medication classes. These dramatic changes in MPR and PDC signify that a subpopulation of patients had resolution of symptoms and a reversal of a psychiatric illness. The percentage of patients that were included in the extreme group of a decreased need for medication was consistently higher than the percentage that experienced an extreme increase in medication use (Table 3.9). This is consistent with our hypothesis that psychiatric pathology is partly driven by genetic alterations of the immune response. It stands to reason that, because all patients included in the analysis had a pre-existing psychiatric diagnosis, if polymorphisms associated with immune genes contribute to this pathology, the balance of overall medication use would be shifted downward.

This indicates that there is a need for more research to be completed, either through randomized controlled trials or prospective analysis. These potential studies would provide additional insight into the relationship between the immune system and psychiatric pathology driven by genetic factors. This initial medication analysis only provides an overview of an association between BMT and psychiatric diagnoses. Prospective patient tracking would enable more detailed follow up with the ability to monitor changes in patient diagnoses directly.

Our control medication class, antihypertensives, had similar results to the medication classes of interest. It is noteworthy that the antihypertensive class had the smallest percentage change for overall MPR and PDC, as well as PDC calculated on a per patient basis. This could mean that although the decrease in antihypertensives required post BMT was statistically different, the change in medication requirement induced by BMT was minor comparatively speaking. Alternatively, a previously identified link

between schizophrenia and hypertension could account for this result. In the schizophrenia GWAS study discussed previously, patients diagnosed with schizophrenia that carried polymorphisms in a specific gene locus were found to also have an association to an adverse effect on cardiovascular health.[49] This analysis is still being conducted, but could provide further correlation of the unknown effects of our immune system and the role it plays in multiple diseases including psychiatric and cardiovascular illness.

Strengths

Most research has focused on mouse models or GWAS studies gathering baseline knowledge rather than applying it to clinical practice. Additional information is focused on humans through case reports rather than specific analysis of patient factors. This project is the first study to explore the impact of BMT on psychiatric conditions at the patient population level using medication adherence and utilization analysis. This study is a first attempt at systematically connecting BMT to psychiatric condition resolution/onset in a human population. Previous reports focus on anecdotal evidence on a case-by-case basis. This study provides the first population analysis associating BMT with decreases in psychiatric medication use and adherence.

This study design of reviewing medication adherence is also one that has not been utilized in the past in regard to this patient population. Medication use, although it may not encompass the overall impact of BMT on the changes in psychiatric disease severity or progression, provides a baseline analysis for how treatment of these conditions is impacted. The study provided an overall understanding of the changes in therapy for patients adjusting to medication requirements after BMT therapy, and the potential change in psychiatric symptoms and/or diagnoses—providing an impetus for further investigation. The overall decrease in medication use reveals that BMT has at a minimum an impact on prescription number and medication requirement while still prompting further investigation into the effect it has on actual diagnostic outcomes.

Limitations

With regard to descriptive statistics, our data did not include age, sex or ethnicity of the patients analyzed in this cohort. Utilizing this information could have helped to provide secondary analysis that may lead to certain patient characteristics having an association with medication use reduction. In future studies, this information could also be analyzed and provide additional data that may pertain to the direct impact of BMT on psychiatric conditions depending on patient factors rather than medication use.

With both MPR and PDC, adjustments in a patient's dose was unaccounted for in this study. For patients with mental health conditions, both individual therapies and medications dosage may be adjusted frequently since psychiatric diagnoses generally require frequent alterations to optimize the appropriate individualized therapy. Although medications within the same drug class and the number of days that a medication was prescribed were accounted for through this study, an individual's dosage adjustments were not. This means that a discontinuation of a specific dose to switch to a different dose would be a change in therapy that is not captured as impacting our overall analysis. Analysis based on medication doses could be utilized in future studies in to order to provide a more complete picture.

Medications utilized for treating psychiatric conditions may also be used for similar comorbidities. For instance, we decided to exclude patients with epileptic diagnoses that were originally included in our analysis. Some medications used for epilepsy, like valproate and lamotrigine, were still included due to their therapeutic use for bipolar/manic depression. However, if patients also had epilepsy that was not formerly diagnosed, these medications could be used for that additional treatment. Therefore, though treatment changes may have been due to a change in a comorbid condition, those changes were captured as if they were due to a change in treatment for the psychiatric diagnosis.

Acute care prescriptions used while patients were hospitalized were not assessed or analyzed because this data was not available in the databases utilized. Because of the multiple comorbidities within our study population, and because of the high likelihood of hospitalization in a subset of patients for the treatment of their psychiatric conditions, periods of hospitalization likely significantly impacted both PDC and MPR results. These

unaccounted hospitalizations could also help explain why the overall adherence rates were fairly low, even prior to BMTs. A way to account for this would be through hospital-specific studies that would include in-patient medications for analysis rather than relying solely on outpatient prescriptions.

A patients' overall wellbeing and the drastic change that takes place before and after BMT could also be a potential reason for the decrease in medication use. Patients requiring this "survival treatment" may also require an extensive medication regimen due to the potential illness and comorbidities being treated prior to BMT. The decrease in all medications could coincide with a patient's improvement in overall health and quality of life, thereby minimizing medication use due to becoming healthier rather than being a direct effect of BMT therapy.

Furthermore, many patients with psychiatric conditions are unable to maintain a steady income. In 2006, it was found that 37% of working-age adults with severe mental illness were uninsured for at least part of the year.[63] Additionally in 2010, approximately 33% of adults on Medicaid met the criteria for having a psychiatric condition.[63] Patients were only included in this study if they had private insurance, which was gathered through our data collected from Truven Health MarketScan® Research Database.[51] This limitation leaves a substantial portion of patients unaccounted for in our population, due to their inability to enroll in private insurance. This means that our results only include a portion of our population, rather than an adequate representation of patients with psychiatric diagnoses that could be further analyzed in future studies.

Future Opportunities

This project provides a baseline understanding of whether or not there are changes to psychiatric illness secondary to BMT with plenty of opportunity for expansion. An additional model may include case studies reviewing patients previously diagnosed with psychiatric conditions undergoing BMT and the potential long-term effects that took place as a result. The previously mentioned study with only seven patients is the only case study article addressing this issue at this time. Prospective studies should be designed to investigate changes in diagnosis and/or symptoms of psychiatric conditions for patients undergoing BMT. However, prospective studies in humans are fraught with

difficulties, including those that are conducted in the challenging population of patients with psychiatric conditions. Our data provides additional evidence of a link between immunity and psychiatric illness, and therefore future clinical studies are warranted, as most of this work has been in animal models.

In addition to medications, investigators could also consider examining patient assessment scores and the changes before and after BMT. These could include PANSS and GAF that were utilized in a case report above as well as Daily Assessment of Symptoms – Anxiety, Generalized Anxiety Disorder 7 (GAD-7), Hamilton Anxiety Scale (HAM-A), Panic and Agoraphobia Scale (PAS) and others.[17] These diverse scales provide different ways to assess symptom management that may not be addressed through medication utilization. Medication utilization only directly provides information regarding changes in therapy while these scoring systems measure patients' symptoms. These could be used in the future to generate additional support for the link as well as provide an explicit link between BMT and resolution of psychiatric conditions.

Conclusions

Overall, the results indicate a statistically significant decrease in both the number and adherence of psychiatric/pain management medications as well as antihypertensive medications as a result of BMT. These decreases reveal that BMT may play a role in positively influencing psychiatric diagnoses as well as chronic pain and cardiovascular conditions. These decreases in medication therapy provide the opportunity to pursue further investigation into the impact of BMT through assessment scores in order to directly track patient symptoms. Though these results are all statistically significant, the clinical significance is inconclusive as the large sample sizes may have been the underlying driver for statistical significance of most primary endpoints. Further investigation is required to verify the clinical significance. This study effectively shows that across all of the observed medication classes, medication therapy decreases post BMT. This decrease may be attributed to unexplored immune system links to psychiatric conditions and/or the effectiveness of BMT increasing overall wellbeing. The interplay between BMT and psychiatric diagnoses is not well understood at this time. Mouse models and GWAS studies have shown a potential link. This study is the first step in

exploring this association in a human population. There is a need to further investigate the long-term effects in this patient population with regard to change in psychiatric conditions after BMT. Treatment of major psychiatric conditions could be revolutionized by BMT if this connection is verified.

Appendices

Appendix A: ICD 9 and 10 Diagnostic Codes for Psychiatric Conditions and BMT

Disease State	ICD-9 CM	ICD-10 CM
Bone Marrow Transplant	V42.81	Z94.81
Encounter for general psychiatric examination, requested by authority	V70.1	Z04.6
Schizophrenia	295.x	F90.x
Suicide Attempt	E950.x	T14.91
Psycho-active Substance Abuse	305.x	F19.x
Opioid-Related Disorders	304.x	F11.x
Bipolar, Manic Depressive and Major Depressive Disorders: recurrent events	296.x	F33.x
Bipolar, Manic Depressive and Major Depressive Disorders: single events	311.x	F32.x
Post-traumatic Stress Disorder	309.81	F43.12
Obsessive-Compulsive Disorder	301.4	R46.81
Generalized Anxiety Disorder	300.02	F41.1
Panic Disorder	300.01	F41.0
Alcohol-Related Disorders	291.x	F10.x
Movement Disorder: stuttering, Tourette's, psychogenic pain	307.x	F95.x

Appendix B: Medication Classes and GPI Codes Indicated for Psychiatric Conditions and Control Medications (antihypertensives)

ADHD Medications

Root Classification	Secondary Classification	Medispan Codes
Adhd/anti-narcolepsy/anti-obesity	Appetite Suppressants	55175x
	Decongestants/Appetite Suppressants	99933x, 41100x, 11926x, 537x
	Stimulants	99806x, 65162x, 54092x, 719x, 591x
	Sympathomimetic amines	63187x, 57664x, 55289x, 54569x, 677x, 527x
	Wakefulness promoting agents	63459x

Antianxiety Agents

Root Classification	Secondary Classification	Medispan Codes
Antianxiety Agents		57866x, 57480x, 55175x, 54124x, 53506x

Anticonvulsant Agents

Root Classification	Secondary Classification	Medispan Codes
Neuromuscular Agents, Anticonvulsants, Mood Stabilizers	Anticonvulsants, mood stabilizers	51672x, 43353x
	Anticonvulsants/Restless Legs Syndrome	68387x, 66105x, 65162x, 55048x, 55045x, 33261x, 21695x, 16590x
	Antiepileptic	76282x, 51079x, 13668x
	Barbiturate anticonvulsants, mood stabilizers	65162x
	Sulfamate-substituted monosaccharide anticonvulsants	43063x

Antidepressants

Root Classification	Secondary Classification	Medispan Codes
Antidepressants	Seasonal affective	63739x, 58016x, 54569x
	SNRIs	68382x. 68788x, 62584x, 63874x, 61392x, 18837x, 33261x, 53002x, 51672x, 33261x. 21695x, 21695x

Antidepressants

Root Classification	Secondary Classification	Medispan Codes
	SSRIs	71335x, 63629x, 62584x, 60429x, 16590x, 58016x, 55700x, 54868x, 47463x, 35356x, 23155x
	Tricyclic antidepressants	406x, 536x, 603x, 61392x, 54274x

Antipsychotics

Root Classification	Secondary Classification	Medispan Codes
Antipsychotics/Antimanic Agent	Antimanic	143x
	Atypical Antipsychotics	99746x, 76282x, 68001x, 67544x, 66105x, 60505x, 49999x, 49848x
	Phenothiazines	51079x, 904x, 725x, 719x, 536x, 378x
	Typical Antipsychotics	99919x

Benzodiazepines

Root Classification	Secondary Classification	Medispan Codes
Benzodiazepines		58016x, 50752x, 904x, 839x, 603x, 403x, 54x, 24x

Hypnotics/Sedatives

Root Classification	Secondary Classification	Medispan Codes
Hypnotics/Sedatives/Sleep Disorders	Imidazopyridines	67544x, 55887x, 43063x,
	Other	49999x, 41163x, 701x, 677x, 363x, 157x

Migraine Medications

Migraine Products	Ergot alkaloids	52054x
	Sympathomimetic drug	62584x
	Triptan/Serotonin Receptor agonists	63801x, 62208x, 540279x, 6026x,4923x,

Opioids

Root Classification	Secondary Classification	Medispan Codes
Analgesics	Opioids	99850x, 67457x, 66336x, 65243x, 63629x, 42358x, 57866x, 55887x, 55700x, 55175x, 54868x, 54274x, 65162x, 52959x, 43386x, 33358x, 16590x, 10544x

Antihypertensives (Control)

Root Classification	Secondary Classification	Medispan Codes
Antihypertensives	ACE inhibitors	74x, 603x, 904x, 13811x, 21695x, 31722x, 52427x, 50090x, 51285x, 55045x, 58118x,60760x, 62584x, 66336x, 67544x, 68788x, 71335x
	alpha-Agonist	38779x
	ARB inhibitors	42291x, 42658x, 54569x, 62332x
	CCBs	70934x, 55289x, 54868x, 54124x, 51138x, 43547xl 43353x, 16590x
	Combination (ARB and Thiazide Diuretics)	228x, 781x, 52343x, 55700x

Antihypertensives (Control)

Root Classification	Secondary Classification	Medispan Codes
	Combination (Beta Blocker and Thiazide Diuretics)	378x, 52555x
	Vasodilators	349x, 64380x

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Vita

Brittany N. Galop, PharmD MS

EDUCATION

Doctor of Pharmacy May 2020
University of Kentucky College of Pharmacy: Lexington, Kentucky

Master of Science in Pharmaceutical Sciences May 2020
Focus in pharmaceutical outcomes and policy
University of Kentucky College of Pharmacy: Lexington, Kentucky

Certificate of Public Health Management May 2020
University of Kentucky: Lexington, Kentucky

PROFESSIONAL EXPERIENCE

Pharmacy Intern Apr. 2016–May 2020
Baptist Health Hospital: Lexington, Kentucky
Supervisor: Michael Anderson, PharmD and Brian Host, PharmD

Pharmacy Intern May–Aug. 2018
Carilion Clinic/Roanoke Memorial Hospital: Roanoke, Virginia
Supervisor: Melissa Hobbins, PharmD

PUBLICATIONS

Galop BN, Fink III JL. The impact of telemedicine on pharmacists and implications for controlled substances. *Pharm Times.* 2017(Dec).

Galop BN, Fink III JL. What the WHO essentials list means for mental health. *Pharm Times*. 2017(Nov).

Galop BN, Fink III JL. What does the 21st Century Cures Act mean for America? *Pharm Times*. 2017(Oct);83:54.

Galop BN, Fink III JL. Emergency preparedness in Kentucky: both physical and mental relief. *Kentucky Pharmacist*. 2017(Sept/Oct);12:5

HONORS AND AWARDS

Dean's List Fall 2016–18; Spring 2019
University of Kentucky College of Pharmacy: Lexington, Kentucky

Alan Wrightson, Sr Endowed Memorial Scholarship Apr. 2019
University of Kentucky College of Pharmacy: Lexington, Kentucky

2019 CPNP Foundation Student Registration Grant Jan. 2019
College of Psychiatric and Neurologic Pharmacists: Lincoln, Nebraska