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Effect of Medication on Cognition: Information from a Clinical Sample using a Semi-Flexible Battery of Common Neuropsychological Tests

Sarah E. Taylor

THE EFFECT OF MEDICATION ON COGNITION: INFORMATION FROM A CLINICAL SAMPLE USING A SEMI-FLEXIBLE BATTERY OF COMMON NEUROPSYCHOLOGICAL TESTS

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Sarah E. Taylor
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B.S., James Madison University, 2013
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To Brandon and Teddy for your love, patience, and understanding, always.

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LIST OF ABBREVIATIONS

ACEI	=	Angiotensin-Converting Enzyme Inhibitor
AED	=	Antiepileptic Drug
AGS	=	American Geriatrics Society
AGS Beers Criteria	=	American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults
Animals	=	Animal Naming
ANOVA	=	Analysis of Variance
ANCOVA	=	Analysis of Covariance
ARB	=	Angiotensin II Receptor Blocker
AVLT	=	Auditory Verbal Learning Test
BMI	=	Body Mass Index
BNT	=	Boston Naming
CCB	=	Calcium Channel Blocker
CDC	=	Centers for Disease Control and Prevention
CHC	=	Cattell-Horn-Carroll
CNS	=	Central Nervous System
CPT	=	Continuous Performance Test
CRP	=	C-reactive protein

CVA	=	Cerebrovascular Accident
DL	=	Dichotic Listening
DRP	=	Drug Related Problem
FAS	=	Controlled Oral Word Association Test
FC	=	Forced Choice
FDA	=	United States Food and Drug Administration
FLT	=	Finger Localization Test
FSIQ	=	Full Scale IQ
FTT	=	Finger Tapping
GLM	=	General Linear Model
HII	=	Halstead Impairment Index (HII)
HRB	=	Halstead-Reitan Battery
IIV	=	Intra-Individual Variability; Overall Test Battery Mean Standard Deviation
IQ	=	Intelligence Quotient
IRB	=	Institutional Review Board
IVA	=	Integrated Visual and Auditory
JLO	=	Judgment of Line Orientation
MANCOVA	=	Multivariate Analysis of Covariance
MAR	=	Missing at Random
MCAR	=	Missing Completely at Random
MCI	=	Mild Cognitive Impairment
MEP	=	Memory Error Patterns

MMSE	=	Mini-Mental State Exam
MNAR	=	Missing Not at Random
MNB	=	Meyers Neuropsychological Battery
NAART	=	North American Adult Reading Test
NCHS	=	National Center for Health Statistics
NHANES	=	National Health and Nutrition Examination Survey
OTBM	=	Overall Test Battery Mean
OTBM *SD*	=	Overall Test Battery Mean Standard Deviation; IIV
OTC	=	Over the Counter
PIM	=	Potentially Inappropriate Medication
POI	=	Perceptual Organization Index
PRI	=	Perceptual Reasoning Index
PSI	=	Processing Speed Index
PVT	=	Performance Validity Test
RCFT	=	Rey Complex Figure Test
RIM	=	Rohling Interpretive Method
SARI	=	Serotonin Receptor Antagonists and Reuptake Inhibitors
SD	=	Standard Deviation
SMD	=	Standard Mean Difference
SMI	=	Severe Mental Illness
SMS	=	Serotonin Modulator and Stimulators
SNRI	=	Serotonin and Norepinephrine Reuptake Inhibitors
SR	=	Sentence Repetition

ss	=	Scaled Score
SSRI	=	Selective Serotonin Reuptake Inhibitors
TBI	=	Traumatic Brain Injury
TCA	=	Tricyclic Antidepressants
TMT	=	Trail Making Test
TMT-A	=	Trail Making Test, Part A
TMT-B	=	Trail Making Test, Part B
TT	=	Token Test
UK	=	United Kingdom
UN	=	United Nations Department of Economic and Social Affairs, Population Division
US	=	United States
VCI	=	Verbal Comprehension Index
VCT	=	The Category Test - Victoria Revision
WAIS	=	Wechsler Adult Intelligence Scale
WAIS-III	=	Wechsler Adult Intelligence Scale, Third Edition
WAIS-IV	=	Wechsler Adult Intelligence Scale, Fourth Edition
WMI	=	Working Memory Index

ABSTRACT

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BACKGROUND: Prescription medications are widely used, particularly among older adults, with 46% of adults overall and 85% of older adults (65 years old and older) using at least one medication (Martin et al., 2019). Three percent of adults overall and 39% of older adults use 5 or more medications, constituting polypharmacy (Kantor et al., 2015). While there are many medications, as well as polypharmacy, that are known to have cognitive effects, many other widely used medications have been inconsistently associated with changes in cognition. Additionally, the degree of change, independent of effects of a possible underlying neurodegenerative process, is unknown. This is problematic for physicians, specifically neuropsychologists, who are tasked with evaluating cognition and providing differential diagnoses for potential cognitive change. OBJECTIVES: The current study sought to evaluate the effects of medication and polypharmacy on global and domain specific cognitive functioning in a broad clinical sample of adults using a comprehensive battery of neuropsychological tests. METHODS: Seven hundred and fifty archival neuropsychological data files were reviewed for inclusion. Four hundred and ninety-seven cases were ultimately retained for analyses (mean age = 40.75, SD = 14.61, range = 18-80 years). Most of the sample identified as

female (52%) and Caucasian (94%). The number of medications used by study participants ranged from 0 to 14 (M = 2.64, SD = 2.50) and 11.3% reported taking 6 or more medications. All participants completed a large flexible battery of common neuropsychological tests, which allowed for calculation of overall test battery performance and cognitive domain specific performances. RESULTS: Two-way Analyses of Covariance analyzed the interaction and main effects of specific medication groups and polypharmacy on global cognitive performance, as measured by the overall test battery mean and intra-individual variability. Significant main effects of analgesics, triptan, polypharmacy on IIV were identified. No significant interaction or main effects were identified for two-way Multivariate Analyses of Covariance evaluating the effects of medication and polypharmacy across nine cognitive domains. CONCLUSIONS: Subjects taking analgesic medications, and medications from the triptans drug class, showed more cognitive variability over the course of a neuropsychological evaluation, compared to those not taking these medications. Additionally, subjects without polypharmacy showed more cognitive variability than those taking more than 5 medications and those who were not taking any medications. Study limitations and clinical implications of these findings are discussed.

CHAPTER I

INTRODUCTION

The percent of adults and older adults in the population is steadily increasing. By 2030, The United Nations Department of Economic and Social Affairs, Population Division (UN; 2019) estimates that in the United States (US), 77% of the population will be over the age of 20 and 37% of the population will be over the age of 50. These are 5% and 11% increases in the size of these age groups since 1990. The UN estimates that these US age cohorts will continue to increase in size over the next 20 years to include 78% and 41% of the total US population, respectively, in the year 2050.

One explanation for the increased population of adult and older adult cohorts in the US is the overall increase in life expectancy, following a reduction in death rates in late life (Zhaurova, 2008). For example, declines in smoking rates have led to fewer deaths due to cardiovascular disease (Silverstein et al., 2001; Stewart et al., 2009). Availability of Medicare coverage for individuals over the age of 65 has improved access to health interventions for older adults in the US, including access to prescription medication (Crimmins, & Beltrán-Sánchez, 2010). Additionally, a greater focus on prevention of disease and evolution of medical treatments have lowered the instances of fatalities due to heart attack, stroke, and cancer (Baigent et al., 2005; Law et al., 2009). However, longer life expectancies do not necessarily equate to a healthier population of adults and older adults.

For example, rates of obesity have increased drastically since the 1980s across all age groups (Flegal et al., 2016; Ogden et al., 2006). Similarly, prevalence rates for arthritis and musculoskeletal problems have been on the rise (Reynolds et al., 1998). Biomarker trends indicate that individuals between the ages of 40 and 64 are being diagnosed and treated for hypertension and high cholesterol more than in previous years (Martin et al., 2010). Additionally, trends of higher C-reactive protein (CRP) levels, an indicator of body inflammation, in men and glycated hemoglobin levels, an indicator of excess sugar and possible uncontrolled diabetes, in women between the ages of 40 and 64 are evident (Martin et al., 2010).

These changes are consistent with data from the Center for Disease Control and Prevention (CDC) showing significant increases in adult obesity since 1999 (Hales et al., 2017). Moreover, evidence from the National Health Interview Survey generally shows increases in heart disease, heart attacks, stroke, cancer, and diabetes in men over 30 and women over 40 (Crimmins & Beltrán-Sánchez, 2010). Further, the rates of comorbidity as well as the number of comorbid diseases prevalent in older adults are significantly higher than in previous decades (Crimmins & Saito, 2000). Recent estimates suggest that most community dwelling older adults are diagnosed with two or more chronic conditions (Barnett et al., 2012). However, for individuals residing in care facilities, the number of comorbid conditions is significantly higher. One study conducted in Germany reported that individuals in residential care facilities averaged 17 chronic conditions (Akner, 2009).

However, not all prevalence rates are rising. Specifically, over the past decade, incidents of high cholesterol and hypertension appear to be declining (Crimmins et al.,

2005; Crimmins et al., 2010). Given the relations between high cholesterol and hypertension with heart disease and stroke (Johnson et al., 2014), the leading and fifth leading causes of death in the US (Murphy et al., 2018), respectively, these findings support a decrease in late life mortality. Yet, in the context of the biomarker trends described above, it is most likely that these declines are attributable to the use of prescription drugs to treat or manage these diseases rather than a reduction in diagnoses of these conditions altogether (Crimmins & Beltrán-Sánchez, 2010).

Thus, while more people are living into older adulthood, disease morbidity appears to be expanding. This fact is supported by the widespread use of prescription medications to both prevent and treat conditions plaguing adults and older adults. A national US survey conducted in 2011 and 2012 indicated that 59% of adults over the age of 20 reported using one or more prescription medications (Kantor et al., 2015). Fifteen percent of these adults reported using 5 or more medications (Kantor et al., 2015). For Americans over the age of 65, 90% reported using one or more prescription medications and 39% reported using five or more prescription medications (Kantor et al., 2015).

These numbers are generally consistent with international trends of medication use. Across all age groups, in the United Kingdom (UK), 43% of patients were prescribed at least one regular prescription medication by their primary care physician and generally averaged four regular prescription medications (Petty et al., 2014). However, when focusing specifically on community-dwelling older adults, data from the UK (Clague et al., 2016; McLean et al., 2017; Petty et al., 2014), Norway (Andersen et al., 2011), and Spain (del Ser et al., 2019) suggest that 70% to 95% of patients used at least one prescription medication and on average took between three and four different drugs or

medications, concurrently. Therefore, most adults and older adults in the US and internationally regularly use medications.

While the use of these medications in pharmacotherapy are ideally effective, safe, and selective in their effects, there is no guarantee that any drug will be without unintended side effects, such as a decline in cognitive functioning (Burchum & Rosenthal, 2016; Jyrkkä et al., 2011; Maher et al., 2014; Martin et al., 2000). For example, opioids (Allegri et al., 2019), anticholinergic medications (Risacher et al., 2016), certain bladder relaxants (Obermann et al., 2013), and various antiepileptic medications (Nevado-Holgado et al., 2016; Park & Kwon, 2008; Stein & Strickland, 1998), have been associated with cognitive decline. Additionally, polypharmacy (use of five or more drugs) and excessive polypharmacy (use of 10 or more drugs) have been associated with changes in cognitive functioning (Jyrkkä et al., 2011; Sordahl et al., 2019).

In the US, a subset of these side effects is identified in clinical trials, prior to general use of the drug, as approved by the Food and Drug Administration (FDA). However, while clinical trials are typically conducted in samples composed of 500 to 5000 patients, patient samples rarely include older adults, patients on multiple regular medications due to comorbidities, or other cognitively vulnerable populations (Boyd et al., 2012; Burchum & Rosenthal, 2016; Cho et al., 2011; McMurdo, 2005). Additionally, only a few hundred patients participating in clinical trials test the prescribed medication for more than 3 to 6 months (Burchum & Rosenthal, 2016).

Therefore, some variations in pharmacokinetics and pharmacodynamics across patient populations and long-term effects of many prescription drugs may not be properly

vetted prior to their widespread use (Katzung, 2018). Further, neither clinical testing nor FDA approval is required for combination medications prior to their public release (FDA, 2017). Instead, FDA investigations into the safety of a combination medication only occur after public health concerns are reported (FDA, 2017).

The combination of high use patterns of prescription medications (Andersen et al., 2011; Clague et al., 2016; del Ser et al., 2019; Denison et al., 2012; Kantor et al., 2015; Kelly et al., 2005; McLean et al., 2017; Petty et al., 2014; Qato et al., 2008) and the limitations in evaluations of the effects of these drugs (Burchum & Rosenthal, 2016; Cho et al., 2011; FDA, 2017) suggests that there are more side effects of using currently available drugs than we are presently aware. Many of these possible side effects may directly or indirectly impact cognitive functioning. This creates a challenge for physicians across professional fields in determining the etiology of changes in a patient's cognitive functioning. Neuropsychologists, in particular, who spend over three-fourths of their time evaluating the cognitive abilities of adults (Rabin et al., 2016), must be able to determine the effects of specific drugs or interactions between multiple drugs to accurately interpret results from neuropsychological assessments. Without accurate and thorough studies evaluating these potential effects on cognitive functioning, implications may include inappropriate diagnosis, delayed treatment of appropriate diagnosis, use of potentially inappropriate medications (PIMs), increased or subsequent adverse drug reactions (e.g., falls or delirium), financial cost of increased medical care, motor vehicle accidents, irreversible cognitive impairments, and financial and psychological costs of loss of employment.

Therefore, to further the understanding of medication effects in the context of neuropsychological assessment, this study will examine the effects of medication on cognition in a clinical sample using a semi-flexible battery of common neuropsychological tests. The following literature review summarizes relevant concepts of clinical pharmacology and information on patterns of medication use. Additionally, this review will explore research regarding the effects of various clinical pharmacology and polypharmacy on cognition and ways to measure these effects.

CHAPTER II

LITERATURE REVIEW

Clinical Pharmacology

The field of clinical pharmacology is concerned with all aspects of how drugs function in humans, where a drug is defined as any chemical that impacts life (Burchum & Rosenthal, 2016). This includes the study of drugs and drug interactions across clinical and non-clinical (i.e., healthy) populations. Therefore, the basic principles of clinical pharmacology apply to the development and testing of new drugs, as well as to the use of established drugs to prevent or treat disease (Katzung, 2018). Theoretically, these basic principles are grounded in a shared goal: to develop and use a drug/drugs to safely and reliably create desired responses, without side effects or unintended interactions. However, the innumerable complexities of the interactions between biophysiology, biochemistry, genetics, psychology, and other processes that contribute to human functioning all but preclude the possibility of ever developing a "perfect drug." Consequently, the primary objective in the medical use of drugs is to maximize the benefits of therapeutics while minimizing harm (Burchum & Rosenthal, 2016; Katzung, 2018).

Ultimately, therapeutic outcomes depend on many different factors that can be related to the patient, the drug, the treating physician, or the surrounding environment. Although, the drug response within the human body is arguably the factor of greatest

consequence, given the primary objective of pharmacotherapy. Specifically, if the response is too high, the drug will accumulate throughout the body, leading to toxicity (Burchum & Rosenthal, 2016). Conversely, if the response is too low, concentrations of the drug in the bloodstream will decrease, leading to possible treatment failure.

In each of these cases, the harm created by the inappropriate intensity of the drug reaction outweighs the benefits. When the strength of the drug is too low, there is no benefit of pharmacotherapeutics. Additionally, given the possibility that drug exposure, and subsequent treatment failure, increases drug-resistance of the disease or diagnosis, a low intensity drug reaction may cause more than minimal harm (Martinez et al., 2012). On the other hand, severe adverse effects have been associated with drug toxicity, such as the development of delirium, dementia, and even death (Moore & O'Keeffe, 1999). Therefore, when a drug is administered, ensuring that the intensity of response will be appropriate is essential to achieving the primary therapeutic objective in clinical pharmacology. Several factors that contribute to variations in the intensity of a drug response, which may lead to overall harmful or negative drug effects, are explored below.

Factors Related to Drug Intensity

Drug Administration.

First, variables related to drug administration can significantly affect the strength of a drug. Specifically, dosage, route of administration, and frequency or timing of an administered medication could lead to very high or very low concentrations of a drug in the bloodstream (Burchum & Rosenthal, 2016; Katzung, 2018). Therefore, specific drug dose regimens that dictate these factors (e.g., 30 mg, once daily, at bedtime, taken orally)

are designed to achieve steady-state drug concentrations that provide the most benefit from therapeutic drug intervention while minimizing drug toxicity (Brandt, 2013; Martinez et al., 2012). However, medication errors contribute to variability in drug dosage, route of administration, and timing that affect the intensity of the drug reaction.

Pharmacokinetics.

Pharmacokinetics, which determine how drugs move into, through, and out of the body in four basic processes (i.e., absorption, distribution, metabolism, and excretion), also plays a role in determining drug reaction intensity (Stahl, 2013). Absorption is the process by which a drug moves from the administration site into the blood (Burchum & Rosenthal, 2016). Distribution is the process by which a drug moves throughout the body, from the blood and into cells. Metabolism is the process by which drugs are altered or transformed by enzymes (i.e., enzymatic alterations) to promote excretion. Excretion is the process by which drugs are removed from the body. Ultimately, these processes work collaboratively to determine the how much of a drug arrives to the sites of action and how long the drug remains at its sites of action (Katzung, 2018). However, factors related to absorption and elimination (i.e., metabolism and excretion) have unique roles throughout this process that impact the intensity of a drug response.

Specifically, the amount of drug that is absorbed following drug administration and how quickly the drug is absorbed are the first factors that contribute to the strength of a drug response. Essentially, higher and more quick absorption leads to greater accumulation of the drug in the body, whereas lower and slower absorption leads to a smaller accumulation of the drug in the body (Burchum & Rosenthal, 2016; Katzung, 2018). The concentration of the drug in the body can be altered again based on the

outcomes of the metabolism. In addition to altering drug compounds to improve excretion, the results of enzymatic alterations can include activation or deactivation of compounds or enhanced effects of an administered drug (Burchum & Rosenthal, 2016). Enzymatic alterations that activate previously inactive compounds (i.e., prodrug) or enhance the effect of the drug may increase the concentration of the drug in the body, potentially to toxic levels (Katzung, 2018). Enzymatic alterations that deactivate drugs, on the other hand, reduce the concentration of the active drug in the bloodstream (Burchum & Rosenthal, 2016).

The pharmacokinetic variables that impact the intensity of a drug response described up to this point are generally inherent to pharmacokinetic processes. However, additional variables that depend on the individual, the drug, and circumstance of pharmacotherapeutics may also impact pharmacokinetic processes and thus, the intensity of a drug response. For instance, age, genetics, frailty, and malnutrition have all been associated with reductions in drug metabolism (Katzung, 2018; Kinirons & O'Mahony, 2004). Therefore, rather than maintaining the concentration of the drug through converting the drug to an inactive form and excreting it at a regular rate, the active drug accumulates. This leads to an increase in the concentration of the drug in the system. Similarly, the process of excretion slows dramatically for individuals with chronic kidney disease and those diagnosed with renal failure, conditions that are most common among individuals over the age of 65 (CDC, 2019). Since excretion primarily occurs in the kidneys, slowed excretion of the drug increases the intensity of the drug response (Burchum & Rosenthal, 2016).

Additionally, specific properties of a drug may allow it to induce or inhibit drug-metabolizing enzymes during the process of metabolism, which in turn impact the drug reaction. If drug-metabolizing enzymes are induced, the concentration of the drug will decline and reduce the intensity of the drug reaction (Burchum & Rosenthal, 2016). Conversely, if drug-metabolizing enzymes are inhibited, then the concentration of the drug will rise and increase the intensity of the drug reaction. Finally, competition for metabolism may occur if two or more drugs utilize the same metabolic pathway (Katzung, 2018). This competition could result in reduced metabolism for one or both/all of the drugs involved, thereby allowing for the drug(s) to accumulate in the system.

Pharmacodynamics.

While pharmacokinetics determine how much of an administered dose gets to its sites of action and how long the drug remains active there, pharmacodynamics dictate the intensity and type of reaction a drug has when it is at its sites of action (Burchum & Rosenthal, 2016). To initiate this process, a drug interacts with either a drug binding receptor or other small molecules. This interaction produces a series of events that lead to the drug response. At this stage, much of the intensity of a drug response is due to the dose-response relationship, which is a drug-specific relationship between the size of the administered dose and the intensity of the drug's response (Katzung, 2018). However, this relationship is moderated by factors such as the functional state of the patient, drug tolerance or sensitivity, and placebo effects (Burchum & Rosenthal, 2016).

Individual Differences.

Patient-specific factors involved in determining the intensity of a drug response explain differences in drug responses between individual patients (Burchum & Rosenthal,

2016). Although some of these factors were discussed above in terms of their relationships with pharmacokinetic processes, individual differences can impact pharmacokinetics and pharmacodynamics more broadly to alter the intensity of a drug response. Generally, these factors are categorized in three domains: physiological variables, pathological variables, and genetic variables.

Physiological variables that moderate the intensity of drug responses include age, gender, weight, hormonal status, diet, and oxidative stress (Bailey, 1983; Burchum & Rosenthal, 2016; Deavall et al., 2012; Katzung, 2018). Pathological variables that moderate the intensity of drug responses include impairment of the liver, impairment of the kidneys, frailty, and chronic brain pathology (Katzung, 2018; Kinirons & O'Mahony, 2004; Moore & O'Keeffe, 1999). Genetic predispositions to drug reactions also moderate the intensity of drug responses (Katzung, 2018). While these individual difference variables do not constitute a comprehensive list of patient characteristics, individual variation must be considered both in terms of individual contributions to drug intensity, as well as with regard to interactions between these differences and pharmacokinetic and pharmacodynamic processes in order to maximize the benefits while minimizing harm in pharmacotherapeutics.

Drug Interactions

A further consideration in pharmacotherapeutics involves drug interactions. This can include interactions among two prescribed drugs. Although an administered drug may also interact with food, tobacco, caffeine, or other substances in the body. When drugs interact, there are three possible outcomes: the effects of one drug intensifies (potentiative), the effect of one drug reduces (inhibitory), or the interactive/combined

effect is a new reaction that is not seen when either drug is used individually (Burchum & Rosenthal, 2016). This is similar to the concept of agonists and antagonists for specific substances but refers specifically to drug interactions. Potentiative and inhibitory outcomes may influence therapeutic effects positively by both increasing therapeutic effects and decreasing adverse effects, respectively (Burchum & Rosenthal, 2016). However, potentiative and inhibitory outcomes could also negatively impact therapeutic effects. Specifically, potentiative interactions may increase adverse effects and inhibitory interactions may reduce therapeutic effects (Burchum & Rosenthal, 2016). Not much is known about the implications of interactions in which a new response, not produced when either drug is used independently, occurs as this outcome is rare (Burchum & Rosenthal, 2016).

Mechanisms of Interaction.

There are four mechanisms in which drugs interact: direct interactions, combined toxicity, pharmacokinetic interactions, and pharmacodynamic interactions (Burchum & Rosenthal, 2016). Direct interactions occur due to the physical or chemical properties of the drugs involved and generally result in both drugs becoming inactive (Burchum & Rosenthal, 2016). Although direct reactions can occur inside the body, water inside the body dilutes a drug following administration, so this is less likely to occur (Burchum & Rosenthal, 2016). Combined toxicity occurs when two drugs that are toxic to the same organ are administered (Burchum & Rosenthal, 2016). This results in greater toxic effects and more injury to the patient than if the drugs were not combined in pharmacotherapeutic treatment.

Pharmacokinetic interactions, on the other hand, can affect any of the four basic pharmacokinetic processes (Burchum & Rosenthal, 2016), although only alterations in metabolism will be specified here given its complexity. All pharmacokinetic interactions either enhance or reduce the primary process for the other drug (see pharmacokinetics section above) and oftentimes have implications for drug treatment. Specifically, in terms of metabolism, some drugs induce or increase the metabolism of other drugs by increasing enzymes that process the other drug (i.e., synthesizing; Katzung, 2018). Ultimately, this can increase the rate of metabolism of the other drug by a factor or two or three in a week-long period (Burchum & Rosenthal, 2016). After an increase in metabolism, the rate of metabolism will not return to normal until after the inducing agent is removed. Conversely, some drugs may decrease metabolism of another drug by inhibiting enzymes that would metabolize the other drug (Katzung, 2018). In some cases, inhibition of drug metabolism can be beneficial, however, generally there are many adverse effects (Burchum & Rosenthal, 2016).

Pharmacodynamic interactions can either occur at the same receptor or at separate receptors and can be potentiative or inhibitory (Burchum & Rosenthal, 2016). Although Burchum and Rosenthal (2016) note that interactions occurring at the same receptor are almost always inhibitory. These types of interactions can have significant implications for drug treatment. For example, interactions occurring at the same receptor may serve to reduce beneficial therapeutic effects or reduce toxicity. Interactions occurring from drugs acting at separate sites can also be potentiative or inhibitory, but only if both drugs influence the same physiological process (Burchum & Rosenthal, 2016).

Clinical Significance.

Overall, drug interaction is another factor in which drug intensity may be altered. However, the specific responses that may occur for any particular interaction are dependent on the therapeutic response and mechanisms of action for each drug involved. Nevertheless, any drug interaction has the potential to impact therapeutic effects. In some circumstances, this can be beneficial, such as when an interaction increases the therapeutic effect of a drug or reduces toxicity. Although, in other circumstances, interactions can be detrimental due to reduced therapeutic effects or increased toxicity.

Awareness of these potential outcomes are particularly important for drugs with a narrow therapeutic range. These drugs are particularly sensitive to interactions, with slight increases in the concentration of the drug leading to drug toxicity and slight reductions in the drug concentration leading to treatment failure (Burchum & Rosenthal, 2016). Additionally, the risk of harmful interactions increases as the number of drugs administered increases. While a large number of important interactions have been identified, allowing for some detrimental effects to be reduced, many more have not been identified (Burchum & Rosenthal, 2016). Therefore, significant risk of harmful effects remains when large numbers of drugs are prescribed and interact.

Regulation of Drugs

Some of the risk of a potential harmful effect is evaluated through assessments of a drug's basic properties, such as pharmacokinetics (i.e., absorption, distribution, metabolism, excretion), drug functioning in healthy participants, and drug functioning in clinical samples, per FDA guidelines (Burchum & Rosenthal, 2016). However, even after a drug is considered "safe" and "effective" by FDA standards (see FDA, 2017) and

approved for general use, questions remain regarding the potential for various side effects (Katzung, 2018). This is particularly true for adults with co-morbidities and older adults, who may be more sensitive to cognitive effects and who are often excluded from participation in clinical trials (Boyd et al., 2012; Cho et al., 2011; McMurdo, 2005). Additionally, the subtlety with which many cognitive effects may occur suggests that it is unlikely for most cognitive changes to be identified during the clinical trial phase of drug testing.

Given these limitations in the regulation of drugs and the sizeable potential for previously undetected cognitive effects accompanying their use, it would follow that many patients and physicians alike would be wary of the widespread use of medications. However, current estimates suggest that this may not be the case (Kantor et al., 2015; Martin et al., 2019). In an effort to elucidate the magnitude of potential risk for cognitive effects of prescription medication, the following section will review patterns of medication use and characteristics of persons who use prescription medications.

Patterns of Medication Use

Prescription Medications Over Time

Despite the need for further testing after FDA approval to fully understand the effects of many commonly used medications, specifically with regard to cognitive side-effects, the use of prescription medications has steadily risen until recent years. In an analysis of data from National Health and Nutrition Examination Survey (NHANES), Kantor and colleagues (2015) found that 51% of adults in the US population were

prescribed one or more medications between 1999 and 2000. Two years later, the proportion of individuals over the age of 20 prescribed at least one medication rose to 54% (Kantor et al., 2015). By 2005 and 2006, Kantor and colleagues found that the prevalence of using any prescription medication for adults in the US was 55%. These estimates are generally consistent with data from Che and colleagues' (2014) survey of prescription medication use in Wisconsinites from 2008 to 2010, in which 54% of Americans between the ages of 21 and 74 reported using at least one prescription medication. The most recent data analyzed from Kantor et al. (2015) was from 2011 and 2012. At that time, 59% of Americans over the age of 20 were prescribed at least one medication (Kantor et al., 2015).

However, there is significant variability in reported rates of medication use across studies. For example, data collected from 2009 to 2011 examining the rates of medication use in community-dwelling adults over the age of 50 found that 69% of participants used one or more prescription medications (Peklar et al., 2014). Contrarily, in a 2010 to 2011 study of medication use in community-dwelling adults between the ages of 62 and 85, approximately 88% used prescription medications (Qato et al., 2016). A third study analyzing data from 2011 found that 75% of adults over the age of 60 were prescribed at least one long-term medication (Petty et al., 2014). While these differences are likely due to a combination of methodological differences and sample specific factors, described in more detail below, the extent of variability in these estimates demonstrates the challenges in comparing rates of medication use across studies.

To date, no known studies examine the rates of prescription medication use combining adult and older adult age groups in the most recent decade to directly compare

with Kantor and colleagues' (2015) previous work. However, a US National Center for Health Statistics (NCHS) brief noted that between 2015 and 2016, 47% of adults between the ages of 20 and 59 reported using one or more prescription drugs (Martin et al., 2019). Alternatively, 85% of adults over the age of 60 reported using one or more prescription drugs (Martin et al., 2019). Overall, the rates of prescription drug use across all ages were lower than rates from nearly a decade prior in 2007-2008 (rates of 46% and 48%, respectively; Martin et al., 2019). When examining adult (20-59) and older adult (60+) age groups separately, slight declines were observed for both adults and older adults (Martin et al., 2019). Although neither of these reductions in prescription drug use from 2007-2008 to 2015-2016 were statistically significant. Therefore, it is possible that rates of prescription medication use are leveling or even declining for adults. Nevertheless, use of prescription medications continues to be very high.

Differences in Use of Medications by Age.

Literature has consistently shown that use of prescription medication increases with age (Che et al., 2014; Kantor et al., 2015; Martin et al., 2019; Petty et al., 2014; Qato et al., 2008). In the US, Qato and colleagues (2008) found that 90% of older adults between the ages of 75 and 85 reported using one or more prescription medications compared to 74% of the youngest group, aged 57 to 64. This is consistent with Gurwitz and colleagues' (2003) findings that older adults are the largest group of purchasers of prescriptions, OTC medications, and dietary supplements.

In a broader sample of adults, Che et al. (2014) found a similar pattern. Only a third of adults aged 21 to 39 reported using at least one prescription medication regularly between 2008 and 2010 compared to almost three-fourths of adults aged 60 to 74. A

subsequent study of data collected in 2011 and 2012 found that 35% of adults between the ages of 20 and 39 used one or more prescription medications, compared to 65% of those between the ages of 40 and 64 and 90% of those over the age of 65 (Kantor et al., 2015). Different rates of prescription drug use were identified in a 2015 to 2016 US NCHS brief, although the pattern remained the same. Specifically, 47% of people between the ages of 20 and 59 reported prescription drug use compared to 80% of people over the age of 60 (Martin et al., 2019). This relationship between age and prescription medication use was also evident in comparisons of medication use by sex and race (Martin et al., 2019).

Differences in Use of Medications by Gender.

For younger adults, between the ages of 20 and 59, prescription medication use was higher among women than men, 56% compared to 37%, according to a NCHS study conducted in 2015 and 2016 (Martin et al., 2019). Women (86%) also showed a higher use of prescription medications than men (77%) in a study conducted in 2005 and 2006 of older adults ranging from 57 to 85 years old (Qato et al., 2008). However, a more recent study found that for adults over the age of 60, there was no difference between men and women in their use of prescription drugs (Martin et al., 2019). When examined across all age groups, this NCHS study found prescription medication use to be higher in women (50%) than men (42%; Martin et al., 2019).

Differences in Use of Medications by Race.

In addition to differences in prescription medication use across age and gender, prescription medication use also varies across race. Overall, use of prescription medication is highest among persons who identified as White (50%), followed by persons

who identified as Black (45%), according to the most recent data from NCHS (Martin et al., 2019). Use of prescription medications is lowest among those who identified as Hispanic (37%) or Asian (33%; Martin et al., 2019). When examining older and younger adults separately, adults between the ages of 20 and 59 showed the same pattern of prescription drug use as the overall sample: 52.4% White, 45.3% Black, 33.6% Hispanic, and 30.2% Asian (Martin et al., 2019). However, no difference in use of prescription medication was observed across racial or ethnic groups for older adults (e.g., people over the age of 60; Martin et al., 2019).

Other Factors Contributing to Differences in Use of Medications.

In addition to age, gender, and race, several other factors have also been associated with differential uses of medications. For example, rates of prescription medication use differed across various levels of education, income, insurance coverage, and Body Mass Index (BMI) in a broad sample of adults over the age of 20 (Kantor et al., 2015). Specifically, of adults reporting "college" as their highest level of education, 61% reported using at least one prescription medication. In contrast, only 57% of adults who reported having less than 12 years of education and adults who reported completing only "some college" reported using one or more medication. Prevalence of medication use also increased with reported family income (Kantor et al., 2015). Of individuals with a family income below the federal poverty level, 49% reported using one or more prescription medications compared to 65% of adults who reported the highest level of family income (above 88,000). Regarding insurance coverage, not surprisingly, only 31% of adults who did not have insurance reported taking prescription medications compared to 57% of adults who had private insurance and 64% of adults who had insurance through

the government (Kantor et al., 2015). However, differences in medication use by insurance coverage was only calculated for individuals under the age of 65 since nearly all adults over the age of 65 participating in this study reported having some form of health insurance.

Lastly, when evaluating medication use based on BMI, Kantor and colleagues (2015) found that 59% of adults with a BMI below 18.5, 52% of adults with a BMI between 18 and 25, and 57% of adults with a BMI between 25 and 30 reported using one or more prescription medications. Additionally, 62% of adults with a BMI between 30 and 35, 68% of adults with a BMI between 35 and 40, and 73% of adults with a BMI over 40 used one or more prescription medications. Based on the CDC recommended classifications for BMI, which indicate normal BMI as BMI between 18.5 and 24.9 (CDC, 2017), findings from Kantor et al. (2015) indicate that adults with a BMI in the obese category were significantly more likely to use medications than individuals with BMIs in the normal range.

Similar results were identified by Qato and colleagues (2008) in their study of medication and dietary supplement use in older adults. Specifically, older adults with more co-morbid conditions, who classified themselves as "nonpoor", and who reported higher levels of education were more likely to use one or more medications. Although, this included use of any combination of prescription, OTC medications, and dietary supplements.

Common Medications

Despite differences in use of medications across demographic variables, Kantor et al. (2015) identified several of the most common prescription medications used by adults

in 2011 and 2012. Overall, antihypertensives (27%), antihyperlipidemic agents (18%), antidepressants (13%), prescription analgesics (11%), antidiabetic agents (8.2%), proton pump inhibitors (7.8%), and thyroid hormones (6.4%) were the most common therapeutic groups of medications prescribed for individuals over the age of 20. Specifically, simvastatin, a lipid modifying agent used to treat high cholesterol (WHO Collaborating Centre for Drug Statistics Methodology [WHO], 2021), was the most commonly reported prescription medication, taken by 7.9% of the sample (Kantor et al., 2015). Lisinopril, levothyroxine, metoprolol, metformin, hydrochlorothiazide, omeprazole, amlodipine, atorvastatin, and albuterol were also among the top 10 medications reported by Kantor et al. study participants.

Qato and colleagues (2016) found that the most common medications for older adults between the ages of 62 and 85 in 2010 and 2011, were nearly identical to those reported by Kantor et al. (2015) for their broader sample of adults. Antihypertensives was the most common therapeutic group of prescription medications, reported by 65.1% of older adults (Qato et al., 2016). Analgesics (54.3%), antihyperlipidemics (50.1%), coagulation modifiers (47.6%), respiratory agents (19.6%), proton pump inhibitors (18.5%), antidiabetic agents (17.8), and thyroid hormones (15.8%) were also among the most common therapeutic groups of medications prescribed to older adults. In terms of specific medications, simvastatin (22.5%), lisinopril (19.9%), hydrochlorothiazide (19.3%), levothyroxine sodium (15.4%), metoprolol (14.9%), amlodipine (13.4%), metformin (12.6%), atorvastatin calcium (9.7%), atenolol (8.5%), and furosemide (8.2%) were most commonly reported (Qato et al., 2016).

However, when Martin et al. (2019) directly compared older and younger adults in the most recent MCHS data from 2015 and 2016, the most common therapeutic group of prescription medication differed. For younger adults, aged 20 to 59, antidepressants were the most commonly reported therapeutic group of prescription medications (Martin et al., 2019). In contrast, the most common therapeutic group of prescription medications for adults over the age of 60 was lipid-lowering drugs (Martin et al., 2019). These differences are not unusual given that different health conditions are more prominent at different stages of life.

Overall, the use of prescription medications is extensive and more prevalent than in previous decades (Kantor et al., 2015; Martin et al., 2019; Qato et al., 2016). While various demographic variables have been associated with medication use, age appears to be the most significant, with older adults reporting higher consumption of prescription medications than younger adults (Che et al., 2014; Kantor et al., 2015; Martin et al., 2019; Petty et al., 2014; Qato et al., 2008). However, many adults use more than one medication (Che et al., 2014; Denison et al., 2012; Freund et al., 2013; Gahche et al., 2017; Kantor et al., 2015; Qato et al., 2016), which as described above, can impact the pharmacokinetics and pharmacodynamics of the prescriptions and potentially lead to detrimental side effects. Therefore, the literature below describes polypharmacy and its prevalence in prescription medication use.

Polypharmacy

Polypharmacy has featured prominently in studies of pharmacology, nursing practice, and treatment of diagnoses and diseases across fields (e.g., neurology, psychiatry, gerontology, endocrinology, and cardiology) given its relationship with drug

related problems (DRPs) that can interfere with treatment or recovery (Viktil et al., 2007). However, no formal definition of polypharmacy has been identified. Some studies define polypharmacy as the use of two or more medications (Frazier, 2005; Fulton & Allen, 2005). Others define polypharmacy as the use of more drugs than appropriate given a patient presentation (Fulton & Allen, 2005; Tjia et al., 2013). Additionally, polypharmacy has been termed the concurrent use of two or more medications that treat the same symptom, illness, or disease, or treatment with two drugs from the same drug class (Brager & Sloand, 2005). The benchmark of five or more medications has also been used in an effort to standardize definitions of polypharmacy with a customary cutoff value (Viktil et al., 2007).

Through an investigation of the cutoff of five or more medications and DRPs in patients admitted to the hospital, Viktil et al. (2007) revealed a linear relationship between number of medications used prior to admittance and number of DRPs. With every increase in number of medications, there was a nearly 9% increase in DRPs. Further, individuals admitted to the hospital with five or more regular medications experienced significantly more DRPs than patients admitted to the hospital with less than five regular medications (Viktil et al., 2007). However, there is no evidence to suggest that this relationship is due to the cutoff of 5 or more medications to identify polypharmacy rather than a function of the linear relationship between number of medications and DRP. This suggests that indicating polypharmacy with a cut off of 5 or more medications may be entirely arbitrary and not serve as an adequate value to differentiate risk for DRPs in research or clinical practice as it was intended. Despite this explanation, many researchers continue to use the cutoff of 5 or more medications to

indicate polypharmacy when discerning high risk patients and in describing various qualities of the samples that fall in this category (e.g., Che et al., 2014; Jyrkkä et al., 2011; Kantor et al., 2015; Qato et al., 2008, Qato et al., 2016).

For example, an investigation into medication use in older adults, Qato et al. (2008) found that over 50% of adults between the ages of 57 and 85 took 5 or more prescription medications, OTC medications, or dietary supplements. Additionally, of those older adults using prescription medications, nearly 70% reported also using OTC medications, dietary supplements, or both (Qato et al., 2008). A follow-up study conducted five years later from 2010 to 2011 examined the use of medication in older Americans between the ages of 62 and 85 (Qato et al., 2016). Rates of polypharmacy for any combination of medications increased from 50% to 67% of older adults who used 5 or more prescription or OTC medications or dietary supplements (Qato et al., 2016).

Prescription Medications

When specifically considering the relationship between prescription medication and polypharmacy, Qato et al. (2008) found that 29% of older Americans between 57 and 85 years old reported using five or more medications. In a follow-up study examining the use of medication in adults between the ages of 62 and 85, Qato et al., (2016) found the rate of polypharmacy for prescription medications increased to approximately 36%. Conversely, in an investigation of prescription medication use in a broader sample of adults over the age of 20, Kantor and colleagues (2015) found that only 15% of adults reported using five or more medications. The variation in these prevalence rates, like that observed for use of at least one prescription medication, is likely due to the differences in the age of the participants across studies.

When stratified by age, prevalence rates for polypharmacy become more consistent across studies. In fact, when Kantor and colleagues' (2015) sample is stratified by age cohorts, older adults over the age of 65 reported the most instances of polypharmacy, with 39% of this group reporting use of five or more prescription medications. Conversely, only 3% of individuals aged 20 to 39 reported using five or more prescription medications (Kantor et al., 2015).

This concept is further exemplified in a study that reviewed instances of prescription drugs recorded in an electronic medical record of adult patients seen in primary care settings (Freund et al., 2013). Patients aged 18-23, 25-34, 35-44, and 45-54 years old were found to have the following rates of polypharmacy: 20%, 29%, 40%, and 55%, respectively. While these rates are slightly higher than those obtained by Kantor et al. (2015), Qato et al. (2008), and Qato et al. (2016), likely due to the number of prescriptions being determined by a medical record system rather than through in-person interviews, the rates of polypharmacy still appear to increase with age much like that of individual medication use.

Like age, gender was also associated rates of polypharmacy. Overall, women between the ages of 21 and 74 were more likely to experience polypharmacy than men, according to data collected between 2008 and 2010 (Che et al., 2014). Specifically, 16% of women reported using five or more prescription medications compared to almost 11% of men (Che et al., 2014). These results are nearly identical to Kantor and colleagues' (2015) report that 16% of women and 13% of men used five or more prescription medications in 2011 and 2012. Similar patterns are observed in older adults in the 57 to 64 and 65 to 74 age groups (Qato et al., 2008). However, individuals from the oldest age

group, composed of individuals between 75 and 85 years old, did not show any differences in polypharmacy across gender (Qato et al., 2008).

Associations between race, BMI, smoking history and rates of polypharmacy have also been identified (Che et al., 2014; Kantor et al., 2015). In a broad study of adults over the age of 20, 17% of adults who identified as white reported taking five or more medications compared to 14% of adults who identified as black (Kantor et al., 2015). When evaluating use of five or more medications based on BMI, Kantor and colleagues found that 18% of adults with a BMI below 18.5, 8.4% of adults with a BMI between 18 and 25, and 12% of adults with a BMI between 25 and 30 reported using five or more prescription medications. Additionally, 17% of adults with a BMI between 30 and 35, 24% of adults with a BMI between 35 and 40, and 29% of adults with a BMI over 40 used five or more prescription medications. Based on the CDC (2017) recommended classifications for BMI, which indicate normal BMI as between 18.5 and 24.9, adults classified as obese were significantly more likely to use medications than individuals with BMIs in the normal range (Kantor et al., 2015). Further, adults who reported a history of smoking were nearly twice as likely to use five or more prescription medications than adults without a history of smoking (Che et al., 2014).

Not surprisingly, family income, health insurance coverage, and being able to identify a regular source of care were also linked with greater use of polypharmacy in prescription medications (Che et al., 2014; Kantor et al., 2015). Family income was negatively related to polypharmacy; meaning that adults reporting lower family incomes were more likely to report taking five or more medications than adults who reported higher incomes (Che et al., 2014; Kantor et al., 2015). Additionally, adults who reported

having insurance through the government (Medicaid or Medicare), having prescription drug coverage, and who identified a location where they typically receive healthcare were more likely to use five or more medications (Che et al., 2014; Kantor et al., 2015).

Overall, use of prescription medication is extensive, and frequently occurs alongside four or more other medications, as is the case in polypharmacy. While these medications are evaluated by the FDA prior to widespread use, that does not mean they are without side effects, particularly with regard to cognition. Additionally, given the limits in assessment of medication side effects prior to FDA approval and release, it is likely that additional side effects are present, including those that affect cognition. The following section details the cognitive effects that have been observed following the use of various medications.

Cognitive Effects of Medications

Ultimately, any medication may cause cognitive effects, such as confusion associated with delirium, if the drug concentration reaches a toxic level (Moore & O'Keeffe, 1999). Although, delirium-like events are not necessary in order for medications to impact cognitive functioning. Many medications have been associated with more subtle changes in cognition, even in studies of relatively young and healthy samples (see Allegri et al., 2019; Nevado-Holgado et al., 2016; Prado & Crowe, 2019; and Prado et al., 2018). However, for individuals who are cognitively vulnerable due to stroke, traumatic brain injury, or advanced age, these effects may cause more significant changes or chronic cognitive impairment (Moore & O'Keeffe, 1999). Further, for individuals who have already been diagnosed with cognitive impairment, this could mean

worsening impairment or a significant enough decline to warrant a diagnosis of dementia (Campbell et al., 2009).

The American Geriatrics Society (AGS) Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (AGS Beers Criteria) provides a specific list of medications that are typically best to avoid in older adults with the goal of reducing their exposure to PIMs that may increase risk of negative effects (Fick et al., 2019). However, decisions regarding pharmacological treatment are not always clear cut, and depending on various situational factors, may still lead to the use of PIMs that increase the risk of drug toxicity or negative drug interactions in older individuals. This, in turn, may produce cognitive impairment. This is of particular concern in cognitively vulnerable populations who may be at a higher risk of using PIMs (Gnjidic et al., 2018; Miller et al., 2017).

Medications of primary concern for both researchers and clinicians are those known to have sedative or anticholinergic effects due to their effect on the central nervous system (CNS). Specifically, anticholinergic effects have consistently been related to the development of cognitive impairment, delirium, and dementia (Campbell et al., 2009; Marvanova, 2016; Moore & O'Keeffe, 1999). The 2019 AGS Beers Criteria provides a strong recommendation to avoid prescribing drugs with strong anticholinergic properties, such as first-generation antihistamines, antispasmodics, and certain antiparkinsonian agents.

Anticholinergics

Cholinergic pathways have long been associated with cognitive functioning, and memory in particular (Campbell et al., 2009; Stein & Strickland, 1998). Therefore, when

this pathway is interrupted, as is the case in the use of anticholinergic drugs, impairments in cognitive functioning may occur. Many explanations have been provided for this relationship, such as increased brain cell death (Del Pino et al., 2016) or synaptic pruning and degeneration (Geula, 1998) at the sites of action for anticholinergic drugs. Although, an anticholinergic drug, or a drug with a strong anticholinergic effect, functions in much the same way as Alzheimer disease pathology. Specifically, these drugs act as antagonists and block muscarinic receptors (Katzung, 2018; Lam, 2017; Lepkowsky, 2016). As a result of this antagonist effect, reactions that are essential to the communication between neurons for adequate attention, memory, and learning are significantly reduced, leading to functional impairments in these cognitive domains (Lam, 2017; Lepkowsky, 2016; Tannenbaum et al., 2012).

Risacher and colleagues' (2016) demonstrated this in a study of anticholinergic medication use, cognitive functioning, and brain atrophy in cognitively normal older adults. Overall cognitive functioning and performance on tasks of immediate memory and executive functioning were significantly lower for patients taking anticholinergic medications compared to patients who were not taking anticholinergic medications (Risacher et al., 2016). Additionally, structural magnetic resonance imaging (MRI) reviled greater brain atrophy in patients taking anticholinergic medications than patients not taking anticholinergic medications, as evidenced by reduced overall cortical volume and enlargement of the lateral ventricles. Further, patients in this study using anticholinergic medications showed reduced cortical thickness in the medial temporal lobe (Risacher et al., 2016), an area known for its involvement in episodic memory and learning (Squire, 2004).

Anticholinergic effects have been documented for amitriptyline, clomipramine, amoxapine, hydroxyzine, digoxin, furosemide, codeine, and chlorpheniramine among others (Marvanova, 2016; Sordahl et al., 2019; see Table 1 for a list of the drug families and therapeutic uses of a subset of common medications that act on anticholinergic pathways). However, use of one anticholinergic drug will not necessarily lead to negative cognitive effects. Rather, it is the collective potency of the anticholinergic effect of the drug/drugs used, or anticholinergic burden, that leads to impairment (Lam, 2017). For example, in Risacher and colleagues' (2016) study, anticholinergic burden was negatively related to overall cognitive function, as well as immediate recall and executive functioning performance. This effect is often more pronounced in older adults, given the reduced number of cholinergic neurons or receptors, in conjunction with various other pharmacokinetic and pharmacodynamic factors compared to younger adults (Campbell et al., 2009).

While medications with strong anticholinergic effects contribute to a large portion of negative cognitive side effects, there are many other ways that medications may impact cognitive functioning. For example, reduced cerebral blood flow (Marvanova, 2016), the creation of neurotoxic metabolites (Kornitzer et al., 2006; Marvanova, 2016), and imbalances in fluids or electrolytes (Marvanova, 2016) have been suggested as possible mechanisms of cognitive dysfunction following the use of certain medications. Although, the potential for cognitive effects of medication depends on the specific pharmacodynamic effect of the drug itself, which can vary as a function of therapeutic use and drug families. Therefore, the cognitive effects of medications from a selection of therapeutic use categories will be reviewed below.

Table 1

Common Medications with Anticholinergic Properties

Therapeutic Use	Drug Family	Drug Name (generic)
Anxiolytic	Benzodiazepine	Alprazolam
Antihistamine	First-Generation H1 Antagonist	Diphenhydramine
Movement Disorder	Central Muscarinic Antagonist	Benztropine
Antidepressant	MRI	Amitriptyline
Antidepressant	SSRI	Paroxetine
Antipsychotic	Atypical Antipsychotics	Quetiapine
Antidepressant	MRI	Clomipramine
Cardiovascular	Antiarrhythmic	Disopyramide
Cardiovascular	Diuretic	Furosemide
Urological	Antispasmodic	Oxybutynin

Note. Adapted from Sordahl et al. (2019) and Marvanova, (2016). MRI = Monoamine Reuptake Inhibitors, SSRI = Selective Serotonin Reuptake Inhibitor. Medication classifications based on the ACT Classification Index from the (WHO Collaborating Centre for Drug Statistics Methodology, 2021).

Antidepressants

The cognitive effects of antidepressants are varied across drug classes or families. Tricyclic antidepressants (TCAs) are widely known for their negative cognitive effects, likely due to the combination of sedative and anticholinergic effects of drugs in this family (Sordahl et al., 2019; Stein & Strickland, 1998). In terms of cognitive effects, TCAs have been associated with impairments in sustained attention, speed of information processing, memory, and psychomotor functioning (Horst & Preskorn 1998; Stein & Strickland, 1998; Tannenbaum et al., 2012). However, in a recent meta-analysis analyzing cognitive effects of antidepressants in depressed and non-depressed samples, TCAs did not significantly impact performance in any cognitive domain for which it was assessed (i.e., sustained and divided attention, immediate and delayed memory, processing speed, and psychomotor functioning; Prado et al., 2018). Given that TCAs

were only assessed in depressed patients, this finding is complicated by the cognitive benefits resulting from the remittance of symptoms of depression.

In the same meta-analysis, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and serotonin modulator and stimulators (SMSs), all showed significant positive effects in several cognitive domains (Prado et al., 2018). Although, the magnitudes of the identified effects were small and only significant in the depressed sample. Therefore, it is possible that these effects are due to the resolution of symptoms of depression and thus, only speak to the cognitive effects of depression. Additionally, in many of Prado and colleagues' analyses, only two or three studies were included, significantly reducing the likelihood of identifying an effect if one is present.

Nonetheless, results from Prado et al. (2018) were significant for small, positive effects of SSRI use on tasks of divided attention, executive functioning, immediate and delayed memory, and processing speed. SNRI use also showed small, positive effects on tasks of divided attention, executive functioning, and delayed memory. SMS use showed small, positive effects for divided attention, processing speed, and delayed memory. No significant effects were observed for selective serotonin reuptake enhancers (SSREs) in the depressed samples. In non-depressed patients, only SSRIs and SNRIs were analyzed, and no significant effects were observed in any cognitive domain (i.e., sustained and divided attention, immediate and delayed memory, expressive language, visual spatial/construction skills, working memory, processing speed, and psychomotor functioning; Prado et al., 2018).

The cognitive effects of trazodone, a serotonin receptor antagonists and reuptake inhibitor (SARI) often used for sleep initiation, have also been evaluated in recent studies. However, the literature is mixed. Following seven days of use, Roth and colleagues (2011) found small but significant declines in performance on tests of short-term memory, verbal learning, and motor functioning in a sample of young adults diagnosed with insomnia. Conversely, Rush et al. (1997) found acute performance on measures of learning and recall for 50 mg, 100 mg, and 200 mg of trazodone did not differ from participants who were administered a placebo, when assessed six-hours following drug administration. In a third study, Camargos et al. (2015) found no changes in overall cognitive functioning, attention, working memory, and processing speed after two-weeks of trazodone use in older adults diagnosed with Alzheimer's disease. However, the participants were significantly cognitively impaired prior to inclusion in the study (mean Mini-Mental State Exam [MMSE] = 11.2/30, where 25 or more indicates cognitive functioning is within normal limits). Due to this impairment, the participants were unable to complete assessments of verbal learning and memory, which significantly limited the possibility of detecting further decline (Camargos et al., 2015).

Overall, most evidence suggests that use of TCAs leads to poorer cognitive functioning (Horst & Preskorn 1998; Stein & Strickland, 1998). Trazadone may negatively impact various aspects of cognitive functioning. However, more literature is needed on the various acute and long-term effects of trazodone use and the potential for cognitive effects in both clinical and non-clinical samples. While there is no clear evidence of a negative effect of other antidepressant medications (i.e., SSRIs, SNRIs, SMSs, SSREs), and some literature suggests SSRIs and SNRIs may have a positive effect

on cognition in depressed samples, more evidence is required to unequivocally make claims regarding the cognitive effects of these drug classes given the limitations of the presently available literature.

Anxiolytics

In terms of anxiolytics, the use of benzodiazepines has often been associated with changes in cognitive functioning across domains, consistent with known sedative and anticholinergic effects (del Ser et al., 2019; Koelega, 1989; Picton et al., 2018; Stein & Strickland, 1998; Tannenbaum et al., 2012). Specifically, reductions in sustained attention, psychomotor speed, speed of information processing, and memory performances have been observed (del Ser et al., 2019; Stein & Strickland, 1998; Tannenbaum et al., 2012). While impairments in memory and attention domains appear to be dose-dependent, they appear to persist over time (Moore & O'Keeffe, 1999; Stein & Strickland, 1998). However, psychomotor slowing appears to return to normal following sustained use due to increased tolerance of sedation effects (Koelega, 1989). Additionally, a recent longitudinal study of cognitively normal older adults found statistically significant reductions in processing speed at a two-year follow-up (del Ser et al., 2019). Although, the effect of this finding was small.

Despite frequent findings of cognitive impairment across a variety of cognitive domains following benzodiazepine use, there continues to be variability in findings of impairment, and discrepancies regarding which domains are affected. Nader and Gowing (2020) demonstrated this in their recent review of literature examining the association between long-term exposure to benzodiazepines and risk of cognitive decline in adults. Of the 14 studies reviewed, only three supported an association between long-term

benzodiazepine use and cognitive impairment with small to medium effect sizes. However, there was no consistency with regard to affected domains across all three studies. Additionally, definitions of long-term use, cognitive domains assessed, cognitive tests within domains, scoring of cognitive tests, and statistical analyses differed across all included studies, likely contributing to the inconsistent results.

In terms of global cognitive functioning, recent studies of the effects of benzodiazepines in elderly populations were also mixed (Nader & Gowing, 2020; Picton et al., 2018). For example, in reviews of studies examining benzodiazepine use in the elderly, only three of nine prospective clinical trials and five of seven case-control studies found significant differences in overall cognitive functioning between individuals prescribed benzodiazepines and controls (Picton et al., 2018). However, of the studies that did not find impairments in global cognitive functioning in individuals using benzodiazepines, many had smaller sample sizes and shorter follow-up periods. A more recent longitudinal study evaluating benzodiazepine use and the risk of cognitive impairment in older adults found that while benzodiazepine use did not increase the risk of the development of dementia, it did increase the risk of milder cognitive impairment (Nafti et al., 2020). Additionally, literature examining the effects of longer acting benzodiazepines indicates that they are more strongly related to cognitive decline in older adults, compared to shorter acting benzodiazepines (Picton et al., 2018). For example, del Ser et al. (2019) found that bromazepam, in particular, was associated with a higher rate of transition to mild cognitive impairment (MCI) from normal cognition compared to other drugs.

The AGS Beers Criteria (2019) note that there is moderate evidence that benzodiazepines increase the risk of cognitive impairment and delirium in older adults and strongly recommend they are avoided. Despite this recommendation, benzodiazepine use remains common in older adults, particularly women, making them especially susceptible to negative cognitive effects of these prescriptions (Olfson et al., 2015; Maust et al., 2016). There is very little evidence regarding the effects of other anxiolytics on cognitive functioning. Although, in a comparison of buspirone, an atypical anxiolytic and a benzodiazepine, buspirone did not show a statistically significant effect on cognitive functioning (Stein & Strickland, 1998). Therefore, no strong conclusions can be drawn regarding the effect of anxiolytics on cognitive functioning.

Analgesics

Overall, use of analgesics, and opioids in particular, have been associated with cognitive deficits across a range of cognitive domains. In some cases, these negative effects have been associated with anticholinergic or neurotoxic effects of drug metabolites, however, that is not always the case (Kornitzer et al., 2006). With the use of opioids, Ersek and colleagues (2004) noted that reductions in psychomotor speed, poor attention, and impairments in memory were commonly cited in the literature. However, a more recent meta-analytic review found impairments in the domains of verbal working memory, cognitive impulsivity, and cognitive flexibility for individuals using opioids compared to healthy controls (Baldacchino et al., 2012). Conversely, Allegri and colleagues' (2019) meta-analytic review of the long-term effects of opioid use on cognition only identified differential performances in the attention domain, with individuals taking opioid medications having a significantly poorer performance than

those taking non-CNS acting medications. In both Baldacchino et al. (2012) and Allegri et al. (2019), the magnitudes of the effects were medium. Additionally, one longitudinal study of opioid use in older adults found that opioid use was associated with global cognitive decline, although this effect was only evident in participants over the age of 75 and did not control for the effect of pain (Puustinen et al., 2011).

Therefore, opioids appear to have a significant effect of cognition, although the specific domains affected may vary. One possible reason for this may be due to the heterogeneity in chemical structures, pharmacokinetics, and pharmacodynamics of the opioids used in these studies. For instance, morphine has been associated with reduced psychomotor speed, verbal processing, and attention, whereas oxycodone has been associated with reduced attention, verbal learning, working memory, and reaction time (Allegri et al., 2019).

Apart from the cognitive effects associated with opioids, little is known about the cognitive effects of other types of analgesics. One study found that beginning naproxen was associated with improved processing speed from a baseline assessment (Obermann et al., 2013). However, given that pain was not controlled for in this study, this improvement may be due to the resolution of pain rather than an effect of the drug specifically. Overall, opioids appear to significantly affect cognitive functioning, particularly in working memory, psychomotor speed, and attention. However, more research into specific medications within this therapeutic group is necessary in order to clarify the domains affected.

Antiepileptics

Impairments in a broad range of cognitive domains have been observed across a variety of antiepileptic medications (Stein & Strickland, 1998). Broadly, long-term use of antiepileptic drugs (AEDs) has been associated with poor performance on tests of attention and concentration, psychomotor functioning, and verbal fluency (Park & Kwon, 2008; Stein & Strickland,1998). Although short term use of AEDs shows less consistent effects on cognitive functioning, likely due to various methodological problems in these studies (Park & Kwon, 2008).

In general, older antiepileptic medications appear to show more diffuse and intense effects than newer medications (Park & Kwon, 2008; Stein & Strickland, 1998). For example, the negative neuropsychological effects of phenobarbital include sedative- and dose-dependent impairments in measured intelligence quotient (IQ; Calandre et al., 1990; Farwell et al., 1992), attention and concentration (see Smith, 1991 for a review), as well as memory and psychomotor speed (MacLeod et al., 1978). Additionally, phenytoin and carbamazepine use are generally associated with impairment in psychomotor speed and slowed verbal responding, respectively (Stein & Strickland, 1998). Yet, there is evidence to suggest topiramate and levetiracetam, two newer AEDs, produce greater reductions in cognitive functioning than any other AEDs. Specifically, Nevado-Holgado and colleagues (2016) found that use of topiramate was associated with the worst reasoning and memory performances of individuals using active CNS medications. Use of levetiracetam, on the other hand, was associated with memory performances that were only slightly better than that of topiramate but poorer than other AEDs and worse reaction time compared to other AEDs (Nevado-Holgado et al., 2016). Therefore, long-

term use of AEDs is consistently related to reduced cognitive functioning across many cognitive domains, although measures of attention and psychomotor speed may be most sensitive to these effects.

Cardiovascular

Overall, findings of cognitive effects of cardiovascular medications across studies are variable, likely suggesting differential effects of specific medications or drug families used in cardiovascular treatments. Specifically, one meta-analysis studying the effect of various antihypertensive medications on cognitive functioning in patients without a history of cerebrovascular disease (e.g., stroke, stenosis, and aneurysm) found a significant positive effect of antihypertensive medication use on overall cognitive functioning (Marpillat et al., 2013). Although the effect size for this finding was small in magnitude and only significant for the first 6 months of therapeutic treatment. In terms of specific cognitive domains, significant positive effects following use of antihypertensive medications were identified for executive functioning, processing speed, attention, and immediate and delayed memory, with effect sizes ranging from .20 to .40 (Marpillat et al., 2013). When analyzed by drug class/drug family, angiotensin II receptor blockers (ARBs) showed the largest benefit compared to a placebo on overall cognition, with a large, adjusted effect size of .6. Angiotensin-converting enzyme (ACE) inhibitor, beta-blockers, and diuretics also showed significant positive effects on overall cognitive functioning, with effect sizes ranging from medium to large (Marpillat et al., 2013).

These results are consistent with results from Nevado-Holgado et al. (2016) that individuals prescribed ACE inhibitors, such as perindopril performed better on a test of reasoning compared to individuals prescribed other antihypertensive medications.

However, poorer reasoning and slowed reaction times were associated with the use of calcium channel blockers (CCBs) and diuretics, such as amlodipine and furosemide, respectively (Nevado-Holgado et al., 2016). Additionally, in a study of medication use in older adults, Obermann et al. (2013) found negative cognitive effects in processing speed and memory domains for starting furosemide between the baseline and one-year follow-up. Despite these findings, del Ser and colleagues (2019) identified significant reductions in the conversion to MCI with the use of angiotensin II antagonists, and Losartan in particular, as well as with the use of hydrochlorothiazide, a diuretic.

One factor that may contribute to the variability in findings across cardiovascular drug families and specific medications is the anticholinergic properties of some of these medications. For instance, some diuretics, antiarrhythmics, vasodilators, CCBs, and beta-blockers (e.g., furosemide, chlorthalidone, hydrochlorothiazide, disopyramide, quinidine, atenolol, captopril, hydralazine, metoprolol, nifedipine, and timolol maleate) have been rated as having possible anticholinergic activity that may contribute to overall anticholinergic cognitive burden (Marvanova, 2016). Further, many drugs (e.g., reserpine, methyldopa, clonidine, prazosin, and digoxin) within this therapeutic group have been associated with the development of delirium and worsening cognitive functions for individuals diagnosed with mild cognitive impairments or dementia secondary to neurotoxicity, imbalance of neurotransmitters in the CNS, fluid and electrolyte imbalances, and decreased cerebral blood flow (Marvanova, 2016). However, these effects are complicated by the improvement in cognitive symptoms or slowing of progressive cognitive dysfunction that results from hypertension and other cardiac-related

diseases. Therefore, further study of the cognitive effects of antihypertensive medications is warranted.

Overall, many medications have been associated with changes in cognitive functioning. Although, these effects do not occur in a vacuum. Rather, these cognitive effects co-occur and interact with factors that contribute to drug intensity and therefore increase the risk of negative therapeutic effects. Older adults, in particular, are at a high risk of these negative cognitive effects. This is due in part to differences in pharmacokinetic processes and pharmacodynamics in older and younger adults (Fulton & Allen, 2005). Specifically, higher rates of liver and kidneys impairments, frailty, malnutrition, and chronic brain pathology in older adults compared to younger adults play a role in elevating this risk for older adults (Burchum & Rosenthal, 2016; Kinirons & O'Mahony, 2004; Moore & O'Keeffe, 1999). Furthermore, older adults have greater rates of comorbidities, and thus, polypharmacy, than younger adults (Barnett et al., 2012; Kantor et al., 2015), which may also contribute to findings of greater cognitive side effects from medication use.

Cognitive Effects of Polypharmacy

Polypharmacy, defined as the concurrent use of two or more or the concurrent use of five or more medications, and excessive polypharmacy, defined as the concurrent use of 10 or more medications (Jyrkkä et al., 2011), have consistently been associated with greater impairment in cognitive functioning (Jyrkkä et al., 2011; Maher et al., 2014; Moore & O'Keefe, 1999; Sordahl et al., 2019). Although most analyses of these effects focus exclusively on the effects of opioids and polypharmacy in older adults.

Specifically, Wright et al. (2009) found that a combined daily dose of medications greater than three standard doses, across various CNS acting medications, was strongly related to overall cognitive decline in older adults. Similarly, the combined use of opioids and any other CNS acting medication (e.g., benzodiazepines and related drugs, antipsychotics, antidepressants, opioids, anticholinergics, and antiepileptics) in cognitively intact older adults was significantly related to global cognitive decline, even after controlling for other factors related to reduced cognitive functioning, such as age, sex, education, and various medical conditions (Puustinen et al., 2011).

A recent meta-analysis evaluating the effects of opioid use found that the combined effects of opioid therapeutic treatment, antidepressants, and/or anticonvulsants was associated with worse performance on measures of attention compared to patients not taking CNS active medications (Allegri et al., 2019). Effect size estimates for this result were in the medium range (SMD: -.62; Allegri et al., 2019). With regard to anticholinergic medications, increased cognitive burden of anticholinergic medications, through the use of multiple anticholinergic medications, significantly increased the risk of negative cognitive effects, such as delirium and dementia (Agar et al., 2009; Boustani et al., 2008; Campbell et al., 2009; Marvanova, 2016; Moore & O'Keefe, 1999; Sordahl et al., 2019).

While it is clear that there is an effect of polypharmacy on cognition, particularly in older adults who are taking multiple CNS active medications, more literature on this phenomenon in younger adults and for non-opioid medications is necessary. Additionally, in most of the studies described above, cognitive ability is evaluated based on a brief, screening measure of global cognition or single brief measures of specific

cognitive domains (e.g., digit-symbol substitution to assess psychomotor speed or digit span to assess working memory). This practice is problematic in that cognitive screening measures are narrow in scope, have relatively low sensitivity, and are generally designed to identify those who may need a more extensive evaluation (Roebuck-Spencer et al., 2017). Given these limitations, the use of the brief screening measures significantly limits the ability to identify possible effects across the full breadth of cognitive domains, particularly if the effects are subtle. Unfortunately, this limitation in the assessment of cognitive functioning is not restricted to the evaluation of cognitive effects with respect to polypharmacy. Rather, this practice appears to be consistent across studies of medication and cognition. Most studies, even those evaluated within meta-analyses, utilize brief screening measures to evaluate overall cognitive functioning. Although, that is not the only measure of cognition available or used by researchers or physicians in the measurement of cognition. The following section will review some of the other measures of cognitive functioning used by researchers and physicians.

Measuring Cognitive Dysfunction

Global Cognition

While most models of cognitive functioning recognize a general, latent factor of cognition, *g*, the most current framework, termed Cattell-Horn-Carroll (CHC; Flanagan & McGrew, 1997), primarily focuses on the assessment of many first order factors, narrow cognitive abilities, that are subsumed by second order factors, or broad cognitive abilities, which are then subsumed by the third order, overall factor. The CHC model has

been extensively evaluated and is widely accepted in its modeling of cognitive abilities, likely due to its foundation in factor analysis (Ackerman & Heggestad, 1997; McGrew, 2009; Schneider & McGrew, 2012; Stankov, 2000). Therefore, the CHC model supports the guiding principles of cognitive assessment.

The structure of the CHC model is hierarchical in nature and assumes that each factor is somewhat independent, suggesting that there is unique variance attributed to each factor, not accounted for by the remaining factors in that order (Flanagan & McGrew, 1997; Strauss et al., 2006). Therefore, given the multifaceted nature of cognition, the most accurate assessment of cognitive functioning should include multifaceted measures and techniques. However, given limitations in available tests, the ability of patients, the time allotted for the assessment constrain evaluations of cognitive functioning, this is not always possible, and therefore brief screening measures are heavily relied upon in research regarding cognition.

One specific measure that has often been used in the assessment of overall cognitive functioning, is the Mini-Mental State Exam (MMSE; Folstein et al., 1975), particularly in relation to medication effects (e.g., Camargos et al., 2015; del Ser et al., 2019; Jyrkkä et al., 2011; Marpillat et al., 2013; Ng et al., 2014; Puustinen et al., 2011; Sordahl et al., 2019; Wright et al., 2009). While various factor structures for this brief, screening measure of cognitive impairment have been identified, including both unidimensional and multidimensional structures, orientation, attention, and memory factors appear to be the most stable (Banos & Franklin, 2002; Jones & Gallo, 2000). However, factors containing items attributed to language functioning, and construction are less stable, and may be sample specific (Strauss et al., 2006).

Therefore, in terms of measurement of second order factors, or broad cognitive domains consistent with models of cognitive functioning, this measure is very limited. Additionally, given the development of this scale to assess cognitive impairment, there is a large ceiling effect for cognitively normal and mildly impaired patients (de Jager et al., 2009; Hoops et al., 2009). Consequently, it may be nearly impossible to accurately detect small to moderate effects of various prescription medications on global cognitive functioning based on the use of this measure. Given the limitation of the MMSE, two additional measures of global cognitive functioning will be reviewed below, which may more accurately capture changes in cognitive functioning due to medication effects.

Overall Test Battery Mean

An Overall Test Battery Mean (OTBM) serves as a demographically corrected overall index of an individual's performance across a battery of neuropsychological tests (Heaton et al., 2001; Miller & Rohling, 2001; Rohling et al., 2003). This is calculated by first converting all raw test scores to standardized scores either through the use of co-normative data or through the use of independently normed data. Scores must then be converted to a common metric (e.g., T-scores, Z-scores, or standardized scores) and subsequently averaged.

Analysis of this index suggests that it is analogous to the Halstead Impairment Index (HII) derived from the standardized Halstead-Reitan Battery (HRB; Reitan & Wolfson, 1993; Rohling et al., 2003). Reliability estimates of this global index in samples with schizophrenia and normal controls suggest that the OTBM is stable over time and generally consistent with Full-Scale IQ (FSIQ) from the Wechsler Adult Intelligence Scale, third edition (WAIS-III; Heaton et al., 2001). Additionally, the OTBM is sensitive

to differential overall cognitive performances by individuals with various classifications of brain injury, groups diagnosed with general medical conditions, groups diagnosed with depression, and poor effort groups (Green et al., 2001). Therefore, the OTBM appears to be a sufficiently valid and reliable measure of global cognitive dysfunction. Given that the calculation of this measure is based on performance across cognitive domains assessed and is not limited to the domains provided within a single test, this index would likely reflect the general ability (*g*) described in the CHC model given adequate measurement of cognitive domains by individual test selection.

However, there are some limitations to this measurement. Specifically, with regard to individuals who may demonstrate impairments in only select cognitive domains. Since the OTBM only provides an index of central tendency for an individual's overall performance, individuals who are highly consistent in their performance across domains would receive the same index score as those who are highly variable, and likely show deficits in select domains. Therefore, cognitive intra-individual variability (e.g. Hilborn et al., 2009) may serve as another measure of global cognitive functioning that is particularly sensitive to subtle cognitive impairments.

Intra-Individual Variability

Cognitive intra-individual variability (IIV) serves as a measure of spread or dispersion for an individual's performance either within a single measure across time (i.e., consistency) or across multiple measures that are in the same metric unit from a single assessment (i.e., dispersion; Hill et al., 2013; MacDonald et al., 2009). Therefore, it can be calculated in many different ways. The method most relevant to the present study is that of dispersion. IIV is calculated by taking the standard deviation (*SD*) around

an individual's OTBM. Thus, greater IIV indicates greater differences in performance across tasks and domains of a neuropsychological assessment, whereas smaller IIV indicates more similar performances across tasks and domains of a neuropsychological assessment.

Several studies of cognitive IIV suggest that this measure is one of CNS dysfunction (Hill et al., 2013; Hultsch & MacDonald, 2004). Specifically, greater IIV has been associated with frontal lobe impairment (Stuss et al., 2003), various dementing illnesses (Ballard et al., 2001; Hultsch et al., 2000; Murtha et al., 2002; Walker et al., 2000), and HIV status (Morgan et al., 2011). Additionally, cognitive IIV has been found to be positively associated with TBI severity (Hill et al., 2013) and experiences of cognitive decline in cognitively normal older adults (Hilborn et al., 2009). Thus, IIV may serve as a sensitive indicator of cognitive integrity when evaluating the potential effects of prescription medication use.

CHAPTER III

STATEMENT OF THE PROBLEM

The use of prescription medications in treating disease, relieving symptoms, and preventing future physical or mental health events is extensive. Particularly, in adults and older adults, who make up a considerable proportion of the population and are at the highest risk of health-related problems. Despite evaluations of most prescription medications prior to FDA approval and general use, risk of additional side effects remains. This is particularly relevant in the case of relatively subtle and long-term effects of prescription drug use in cognitively vulnerable populations, who are often excluded from clinical trials (Boyd et al., 2012; Cho et al., 2011; McMurdo, 2005). Therefore, the potential for patients to experience meaningful changes in cognitive functioning following prescription medication use is very high, particularly for patients who use multiple drugs.

This issue is highly relevant for physicians, specifically neurologists and neuropsychologists. Without a clear understanding of the effects of medication groups and specific medications, these physicians are unable to adequately clarify diagnoses, make treatment recommendations, and inform prognoses of patients reporting cognitive changes due to their reliance on patterns of performance on cognitive testing (Schoenberg & Scott, 2011). Moreover, while the cognitive effects of some of these commonly prescribed medications have been elucidated in recent years in both cross sectional and

longitudinal studies, several limitations to the existing body of literature remain.

First, few studies examine cognitive effects of medication or polypharmacy in broad clinical samples, limiting the generalizability of results. Second, across studies of the effects of medication on cognitive functioning, many psychiatric, neurological, and general medical diagnoses were inconsistently controlled for (e.g., del Ser et al., 2019 and Obermann et al., 2013). By not adequately controlling for these potential confounding variables, it is impossible to tease out the effects of pharmacotherapeutics from disease/diagnosis effects in these studies. Third, the existing literature on the effects of medication on cognition has generally avoided evaluations of a potential interaction effect with polypharmacy by statistically controlling for possible effects by entering the number of medications prescribed as a covariate in analyses (e.g., del Ser et al., 2019; Nevado-Holgado et al., 2016; Wright et al., 2009). While these types of analyses provide valuable information regarding the individual effects of medication and polypharmacy to cognitive performance, the results are not necessarily generalizable to a significant proportion of the population who use multiple medications concurrently.

Lastly, studies of medication effects on cognition generally restrict investigations to a few screening tests of overall functioning or evaluation of limited domains of cognitive functioning (e.g., del Ser et al., 2019; Jyrkka et al, 2011; Nevado-Holgado et al., 2016; Obermann et al., 2013; Wright et al., 2009). Though these narrow investigations have identified effects for some variables, a more thorough measurement of cognition may detect more subtle effects of altered cognitive functioning. Additionally, questions remain regarding the effects of medications and polypharmacy on common neuropsychological measures of global and domain-specific functioning across

a variety of cognitive domains.

The Present Study

The present study sought to add to and extend the literature regarding effects of medications and polypharmacy on cognition in a broad clinical sample (e.g., TBI, vascular/cerebrovascular accident [CVA], encephalitis, mental health diagnoses, etc.). Specifically, the present study consisted of a thorough evaluation of the independent and collaborative effects of medications and polypharmacy on cognitive functioning in both global and specific domains, as measured by a standardized battery of common neuropsychological tests. Given this objective, three primary aims were explored: (1) the effects of medications and polypharmacy on global cognitive functioning, as assessed by the OTBM; (2) the effects of medications and polypharmacy on global cognitive functioning, as assessed by variability in performance across cognitive domains (IIV); and (3) the effects of medications and polypharmacy on performance in specific cognitive domains.

Hypotheses

The purpose of this dissertation is to address the following aims/hypotheses:

Aim One.

To examine the effects of medication use and polypharmacy on global cognitive functioning, as assessed by OTBM, two-way Analyses of Covariance (ANCOVAs) were used to evaluate the interaction and main effects of medication use and polypharmacy on the OTBM. Specifically, these analyses were used to determine if there was an interaction between medication use and polypharmacy level on OTBM, if there were

differential effects of medication use on the OTBM, and if there were differential effects of levels of polypharmacy on OTBM. To isolate the effects of medication use, levels of polypharmacy, and their potential interaction, psychiatric, neurological, and general medical diagnoses, as well as estimated premorbid functioning were each entered as covariates. Given this objective the following hypotheses were tested:

1.1 There is a significant interaction between medication use and level of polypharmacy on OTBM.

1.2 The OTBM of individuals using a medication is significantly different from the OTBM of those not using the medication.

1.3 The OTBM of at least one polypharmacy level is significantly different from the other polypharmacy levels.

Aim Two.

To examine the effects of medication use and polypharmacy on global cognitive functioning, as assessed by IIV (see the Calculation of IIV section below), two-way ANCOVAs were used to evaluate the interaction and main effects of medication use and polypharmacy on IIV. Specifically, these analyses were used to determine if there was an interaction between therapeutic group and polypharmacy on IIV, if there were differential effects of medication use on IIV, and if there were differential effects of polypharmacy on IIV. To isolate the effects of medication use, levels of polypharmacy, and their potential interaction, psychiatric, neurological, and general medical diagnoses, as well as estimated premorbid functioning were each entered as covariates. Given this objective the following hypotheses were tested:

2.1 There is a significant interaction between medication use and level of

polypharmacy on IIV.

2.2 The IIV of individuals using a medication is significantly different from the IIV of those not using the medication.

2.3 The IIV of at least one polypharmacy level is significantly different from the other polypharmacy levels.

Aim Three.

To examine the effects of medication use and polypharmacy on domain-specific cognitive functioning, two-way Multivariate Analyses of Covariance (MANCOVA) were used to evaluate the interaction and main effects of medication use and polypharmacy on the following cognitive domain means: Attention/Working Memory, Processing Speed, Verbal Reasoning, Visual Reasoning, Verbal Memory, Visual Memory, Executive Functioning, Dominant Motor and Sensory Functioning, and Non-Dominant Motor and Sensory Functioning. Specifically, these analyses were used to determine if there was an interaction between medications and polypharmacy on each cognitive domain mean, if there were differential effects of medication use on each cognitive domain, and if there were differential effects of polypharmacy on each cognitive domain mean. Given this objective the following hypotheses were tested:

3.1 There is a significant interaction between medication use and polypharmacy on a domain-specific performance (e.g., domain mean).

3.2 The domain mean of individuals using a medication is significantly different from the domain mean of those not using the medication.

3.3 The domain mean of at least one polypharmacy level is significantly different from the other polypharmacy levels.

CHAPTER IV

METHODOLOGY

Prior to data collection, this study was approved by the University of South Alabama Institutional Review Board (IRB; see Appendix A). Archival data from two practicing neuropsychologists, located in the Midwestern and Southeastern US, who utilized the Meyers Neuropsychological System (MNS; Meyers, 2013) were utilized in this study. Given that the study was retrospective nature and there was no foreseeable risk, informed consent was not necessary from study participants.

All patients were evaluated between 1990 and 2020. At the time of their assessment, participants completed a clinical interview and a comprehensive flexible battery of neuropsychological tests, which included tests from the Meyers Neuropsychological Battery (MNB; Meyers & Rohling, 2004): subtests from the WAIS-III (Wechsler, 1997) or Wechsler Adult Intelligence Scale IV (WAIS-IV; Wechsler, 2008); Trail Making Test (TMT; Reitan & Wolfson, 1985); Judgement of Line Orientation (JLO; Benton et al., 1983a); Finger Tapping (FTT; Reitan & Wolfson, 1985); Finger Localization Test (FLT; Benton et al., 1983b); Token Test (TT; Spreen & Strauss, 1998); North American Adult Reading Test (NAART; Spreen & Strauss, 1998); Sentence Repetition (SR; Spreen & Strauss, 1991); Controlled Oral Word Association Test (FAS; Spreen & Strauss, 1998); Animal Naming (Animals; Spreen & Strauss, 1998); Boston Naming (BNT; Spreen & Strauss, 1998); Dichotic Listening (DLT; Meyers et al., 2002;

Roberts et al., 1994); Auditory Verbal Learning Test (AVLT; Spreen & Strauss, 1998); Rey Complex Figure Test (RCFT; Meyers & Meyers, 1995); The Category Test - Victoria Revision (VCT; Spreen & Strauss, 1991); and Forced Choice (FC; Brandt et al., 1985).

Inclusion and Exclusion Criteria

Cases were only included in the study if participants were over the age of 18, if medication information was included in the record, and the record contained sufficient (e.g., at least 20%) of the study variables. Given the likelihood that follow-up or re-evaluation data could unintentionally overly influence statistical analyses, these cases were excluded from the study. Further, due to the distinct lower limit of standardized measurement on neuropsychological tests, subjects with premorbid estimations or an OTBM below the second percentile were not included in the study. Lastly, cases were excluded from the study on the basis of failed validity tests or if they had a diagnosis of malingering.

With regard to validity testing, the generally accepted standard indicating invalid test performance is two or more failed validity measures over the course of a neuropsychological evaluation (Larrabee, 2008; Meyers & Volbrecht, 2003; Meyers et al., 2011). However, more recent literature indicates that many commonly used cut-offs for performance validity tests (PVTs) may not be appropriate for use in cognitively impaired samples due to high false-positive rates (McGuire et al., 2019; Martin et al., 2020). Instead, a standard of three or more failed PVTs over the course of a neuropsychological evaluation has been suggested as a more appropriate indicator of

invalid performance in cognitively impaired samples (Martin et al., 2020). Therefore, if a subject was not diagnosed with cognitive impairment and failed two or more validity tests, they were excluded from the study. Contrarily, if the subject was diagnosed with cognitive impairment and the patient failed three or more PVTs, they were excluded from the study.

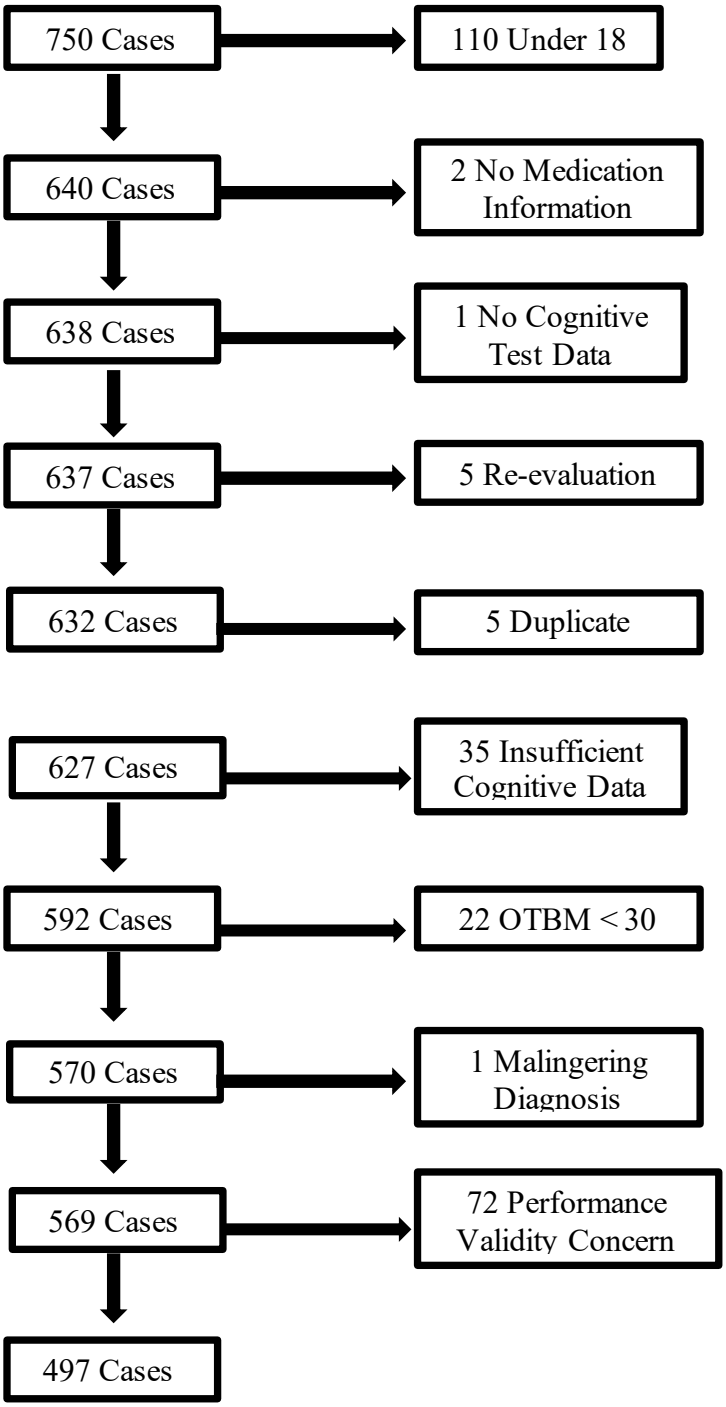
Participants

Seven hundred and fifty archived data files were reviewed for inclusion in this study. Of these cases, 110 subjects were under the age of 18 and were excluded. Of the remaining cases, two did not contain medication information, one did not include any cognitive test data, five cases were re-evaluations, and five cases were duplicate entries and therefore were excluded. An additional 35 cases were excluded due to containing insufficient cognitive data to calculate at least 20% of the study outcome variables.

Of the remaining 592 cases, 22 cases were excluded due to having an OTBM below the second percentile (e.g., $T < 30$). Further, one case file listed a diagnosis of "malingering" and was excluded. Seventy-two additional cases were excluded due to concerns for performance validity as described above. The remaining 497 cases were retained for inclusion in the study. See Figure 1 for a visual representation of the screening process.

Figure 1

Screening Process and Exclusion Criteria for Archival Case Review



Note. OTBM = Overall Test Battery Mean.

Table 2 presents characteristics of the final sample. As can be seen, the final sample had a mean age of 40.75 (*SD* = 14.61, range = 18-80 years old). Average years of education was 12.93 (*SD* = 2.36). Fifty-two percent of the sample identified as female. A majority of the sample identified as Caucasian (*n* = 468, 94.0%). Number of medications used by each subject ranged from 0 to 14 medications (*M* = 2.64, *SD* = 2.50). Approximately 11% of cases had polypharmacy, as defined as using six or more medications. Table B.1 and Table B.2 detail the diagnoses and medications for sample participants, respectively. Additionally, given that medications with strong anticholinergic properties come from a variety of therapeutic use categories and medication families, medications with strong anticholinergic properties used by sample participants are also provided in table B.3. Table 3 details overall cognitive performance for the sample.

Of note, 47 subjects (9.5%) in this sample were considered "older adults," as defined as age at or above 65 years, at the time of the evaluation. Given the generally small subsample of older adults, these groups were combined for all analyses. However, much like the literature on medication use, medication use significantly differed across these stages of life [$\chi^2(2, 497) = 17.75$, $p < .001$). Specifically, 17.8 % of adults reported not taking any medications, 72.4% of adults reported taking 1-5 medications, and 9.8% of adults reported taking six or more medications (e.g., polypharmacy). For older adults on the other hand, all subjects were taking at least one medication. Approximately 75% of older adult subjects reported taking 1-5 medications. The remaining 25.5% of older adult subjects reported taking 6 or more medications (e.g., polypharmacy). Performance on cognitive measures did not differ between adults and older adults in the sample

[$t_{OTBM}(495)=0.30$, $p=.384$; $t_{attention}(492)=0.97$, $p=.166$; $t_{processing\ speed}(491)=-0.18$, $p=.430$; $t_{verbal\ reasoning}(493)=1.03$, $p=.1.52$; $t_{visual\ reasoning}(494)=1.27$, $p=.102$; $t_{verbal\ memory}(488)=-0.92$, $p=.179$; $t_{visual\ memory}(479)=0.12$, $p=.451$; $t_{executive\ functions}(495)=0.43$, $p=.333$; $t_{dominant\ motor}(461)=-0.69$, $p=.246$; $t_{non\text{-}dominant\ motor}(460)=-1.0$, $p=.150$; $t_{IIV}(473)=-0.40$, $p=.345$].

Table 2

Characteristics of the Final Sample

	Total Sample	Adult	Older Adult
Variable	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Age	40.8 (14.6)	37.9 (12.1)	67.8 (6.5)
Education	12.9 (2.4)	12.9 (2.3)	13.4 (3.1)
Gender	*n* (Valid %)	*n* (Valid %)	*n* (Valid %)
Male	237 (47.7%)	212 (47.1%)	25 (53.2%)
Female	259 (52.1%)	237 (52.7%)	22 (46.8%)
Ethnicity			
Asian/Asian American	3 (0.6%)	3 (0.7%)	0 (0.0%)
Black/African American	13 (2.6%	12 (2.7%)	1 (2.1%)
Caucasian	467 (94.0%)	421 (93.6%)	46 (97.9%)
Other	13 (2.6%)	13 (2.9%)	0 (0.0%)
Medication Use			
No Medications	80 (16.1%)	80 (17.6%)	0 (0.0%)
1-5 Medications	361 (72.6%)	326 (72.4%)	35 (74.5%)
Polypharmacy (6+)	56 (11.3)	44 (9.8%)	12 (25.5%)
Forensic Evaluation	120 (24.1%)	114 (25.3%)	6 (12.8%)
PVT Failures			
0	263 (52.9%)	233 (51.8%)	30 (63.8%)
1	208 (41.9%)	194 (43.1%)	14 (29.8%)
2	26 (5.2%)	23 (5.1%)	3 (6.4%)
Neuropsychology Practice			
Midwestern	434 (87.3%)	393 (87.3%)	41 (87.2%)
Southeastern	63 (12.7%)	57 (12.7%)	3 (12.8%)

Note. $n = 497$. *M* = mean. *SD* = Standard Deviation. n = frequency. Due to missing data across variables, frequencies of variables may not add up to the total sample size. PVT = Performance Validity Test.

Table 3
Summary of Cognitive Performance for Sample

	n	*M*	*SD*
Premorbid Estimate	485	46.5	4.3
OTBM	497	44.5	5.5
IIV	475	9.7	2.4
Attention/Working Memory	494	44.3	6.9
Processing Speed	493	45.1	7.7
Verbal Reasoning	495	45.6	7.0
Visual Reasoning	496	45.1	6.9
Verbal Memory	490	42.1	10.7
Visual Memory	481	43.8	10.5
Executive Functioning	497	45.3	7.0
Dominant Motor Function	463	46.8	8.3
Non-Dominant Motor Function	462	46.3	7.7

Note. N = 497. Sample sizes differ across variables due to missing values. *n* = sample size. *M* = mean. *SD* = Standard Deviation. OTBM = Overall Test Battery Mean. IIV = Intra-Individual Variability. OTBM and domain means are presented as T Score values.

Measures

Meyers Neuropsychological Battery

All study participants completed the MNB (Meyers & Rohling, 2004) at the time of their assessment. The MNB, is a semi-flexible battery of common neuropsychological tests that are presented in a standard order. The tests that make up the core of this battery have been shown to be sensitive to brain injury (Meyers & Rohling, 2009; Meyers & Rohling, 2004; Volbrecht et al., 2000) and they rank among the most common tests used by clinical neuropsychologists overall (Rabin et al., 2016).

The following tests are part of the MNB core measures: Block Design, Similarities, Digit Span, Arithmetic, Information, Coding, and Picture Completion from

the WAIS-III/IV (Meyers et al., 2013; Pilgrim et al., 1999), TMT (Reitan & Wolfson, 1985), JLO (Benton et al., 1983a), FTT (Reitan & Wolfson, 1985), FLT (Benton et al., 1983b), TT (Spreen & Strauss, 1998), NAART (Spreen & Strauss, 1998), SR (Spreen & Strauss, 1991), FAS (Spreen & Strauss, 1998), Animals (Spreen & Strauss, 1998), BNT (Spreen & Strauss, 1998), DLT (Meyers et al., 2002; Roberts et al., 1994), AVLT (Spreen & Strauss, 1998), RCFT (Meyers & Meyers, 1995), VCT (Spreen & Strauss, 1991), and FC (Brandt et al., 1985). Scores derived from performance on these tests assess the following cognitive domains: Attention/Working Memory, Processing Speed, Verbal Reasoning, Visual Reasoning, Verbal Memory, Visual Memory, Executive Functioning, and Dominant and Non-Dominant Motor and Sensory Functioning (Lezak et al., 2012; Meyers & Rohling, 2009; Strauss et al., 2006).

Given the semi-flexible nature of the MNB, other tests were added to the core MNB and/or were substituted for a core test at the discretion of the supervising neuropsychologist at the time of the assessment and, subsequently, factored into the calculation of study variables (e.g., OTBM, IIV, and cognitive domain means). Eleven additional neuropsychological tests were used across the sample. However, each of these tests was used for ≤ 5% of sample participants. Given this, for concision, only MNB core tests are described below. However, all tests (core and supplemental) used for sample participants and to which cognitive domain they assessed when administered are listed in Table B.4.

Wechsler Adult Intelligence Scale.

The Wechsler Adult Intelligence Scale (WAIS) is a measure of intellectual functioning in older adolescents and adults. The two most recent versions, WAIS III and

WAIS IV, are composed of 10 core subtests that allow for the calculation of a FSIQ and four index scores: verbal ability (VCI), perceptual ability (POI or PRI), working memory (WMI), and processing speed (PSI; Wechsler, 1997; Wechsler, 2008). Internal consistency reliability is very high for the FSIQ, index scores, and core subtests. Further, subtest specificity is adequate across core subtests, an indication of the proportion of subtest variance that is reliable and unique to the subtest (Strauss et al., 2006).

A short form of each version of the WAIS (III or IV) was used as part of the MNB, which includes the Block Design, Similarities, Digit Span, Arithmetic, Information, Coding, and Picture Completion subtests (Meyers et al., 2013). Each of the subtest comprising the short version is known to be sensitive to various forms of brain dysfunction (see Strauss et al., 2006). Additionally, index scores and FSIQ calculated from this abbreviated version correlate highly with the full-length scores, correlations range from .92 to .99 (Meyers et al., 2013; Pilgrim et al., 1999). Effect sizes calculated from comparisons of scores from the short form to the original are negligible (Meyers et al., 2013). Therefore, the short form of the WAIS III/IV appears to adequately assess IQ and index performances.

With regard to the specific subtests, block design is a measure of perceptual reasoning and visual spatial construction, in which patients are asked to arrange blocks to match a picture. Similarities is a measure of verbal abstraction, in which the participant is asked to describe how two words are alike. Digit Span and Arithmetic are measures of basic attention and working memory in which patients are asked to sequence progressively longer strings of digits and quickly solve mathematics-based word problems, respectively. Digit Symbol/Coding is a measure of visual attention, learning,

and processing speed, in which the patient decodes numbers based on a key. Information is a measure of crystallized knowledge, attention, and long-term verbal recall, in which patients are asked to answer questions of general knowledge. Picture completion is a measure of visual perception, in which the patient is asked to quickly identify what piece of various pictures was removed.

As can be seen from Table B.4, block design was part of the visual reasoning/perceptual organization MNB domain (Meyers & Rohling, 2009; Volbrecht et al., 2000; Wechsler, 1997; Wechsler, 2008). Similarities was part of the verbal reasoning/verbal comprehension MNB domain (Meyers & Rohling, 2009; Volbrecht et al., 2000; Wechsler, 1997; Wechsler, 2008). Digit Span and Arithmetic were part of the attention/working memory MNB domain (Meyers & Rohling, 2009; Volbrecht et al., 2000; Wechsler, 1997; Wechsler, 2008). Digit Symbol/Coding was part of the processing speed MNB domain (Meyers & Rohling, 2009; Volbrecht et al., 2000; Wechsler, 1997; Wechsler, 2008). Information was part of the verbal reasoning/verbal comprehension MNB domain (Meyers & Rohling, 2009; Volbrecht et al., 2000; Wechsler, 1997; Wechsler, 2008). Picture completion was part of the visual reasoning/perceptual organization MNB domain (Meyers & Rohling, 2009; Volbrecht et al., 2000; Wechsler, 1997; Wechsler, 2008).

Trail Making Test.

TMT is a two-part, timed task that first involves drawing a line to connect a sequence of numbers in ascending order (Part A), then drawing a line connecting both numbers and letters in ascending order by switching between connecting numbers and letters (i.e., 1-A-2-B; Part B; Reitan & Wolfson, 1985). TMT Part A serves as a measure

of attention and concentration, whereas Part B serves as a measure of sequencing and mental set shifting (Volbrecht et al., 2000). Each part of the TMT is highly sensitive to cognitive dysfunction across a range of populations, particularly those with deficits in attention and frontal lobe functions (Greenlief et al., 1985; Hervey et al., 2004; Mathias & Wheaton, 2007; Mitrushina et al., 2005; Reitan, 1958; Roca et al., 2013; Ruffolo et al., 2000; Segalowitz et al., 1992). As indicated in Table B.4, TMT A was part of the processing speed MNB domain, whereas TMT B was part of the executive functioning MNB domain (Meyers & Rohling, 2009; Strauss et al., 2006).

Judgement of Line Orientation.

JLO is a 30-item measure of visual perception in which patients compare and identify identically oriented lines from lines that have been shortened (Benton et al., 1983a). Split-half reliability for the JLO is high, ranging from .84 to .91, and test-retest reliability is .90 (Strauss et al., 2006). JLO performance is highly related to performance on visual-spatial subtests of the WAIS (Strauss et al., 2006). Impairments on this test are associated with lesions in the right posterior parietal region (Benton et al., 1983a; Tranel et al., 2009). As indicated in Table B.4, JLO was part of the visual reasoning/perceptual organization MNB domain (Meyers et al., 2009).

Finger Tapping.

FT, also known as the finger oscillation test, is a measure of psychomotor speed and persistence in which a patient rapidly taps their index finger on their dominant hand for 10 seconds (Reitan & Wolfson, 1985). The same procedure is subsequently used on the non-dominant hand. Reliability coefficients across studies is variable, with some coefficients as low as .58 (Strauss et al., 2006). Although, most reliability appears to

generally be between .77 and .94 (Lezak et al., 2012). FTT demonstrates strong convergent and discriminant validity, as evidenced by high correlations with performance on the Purdue Pegboard Test, another measure of psychomotor functioning requiring precise finger movements, and low correlations with grip strength and the processing speed index from the WAIS III (Strauss et al., 2006). As can be seen in Table B.4, FTT performance for the dominant hand was part of the dominant motor and sensory MNB domain, whereas FTT performance for the non-dominant hand was part of the non-dominant motor and sensory MNB domain (Meyers, 2013).

Finger Localization Test.

The FLT is a measure of tactile identification in which a patient identifies and names the finger indicated by the examiner (Benton et al., 1983b). This test is composed of three parts, in which the patient identifies the fingers touched by the examiner, then identifies the fingers touched by the examiner when their hand is hidden from view, then identifies pairs of fingers touched by the examiner simultaneously. Bilateral impairments on the FLT have been associated with lesions in the left posterior perisylvian region (Benton et al., 1983b). However, unilateral and contralateral impairments have been more associated with right hemisphere lesions (Gainotti & Tiacci, 1973). As indicated in Table B.4, FLT performance for the dominant hand were part of the dominant motor and sensory MNB domain, whereas FLT performance for the non-dominant hand were part of the non-dominant motor and sensory MNB domain (Meyers, 2013).

Token Test.

The TT assesses receptive language and comprehension of instructions through the administration of 39 increasingly complex commands (Spreen & Strauss, 1998).

Internal reliability for the TT is high, coefficients ranging from .90 to .92 (Spellacy & Spreen, 1969). The TT correlates highly with other measures of receptive language, correlation of .71 with the Peabody Picture Vocabulary Test (Lass & Golden, 1975), suggesting high construct validity. The token test is sensitive to language disorders and focal left-hemisphere lesions (Strauss et al., 2006). As can be seen in Table B.4, TT was part of the verbal reasoning/verbal comprehension MNB domain (Meyers & Rohling, 2009).

North American Adult Reading Test.

The NAART is a 35-item measure of premorbid intellectual ability, in which a patient reads printed words (Spreen & Strauss, 1998). Reliability estimates are above .90 (Raguet et al., 1996; Uttl, 2002) and predictive validity FSIQ and verbal comprehension is high, correlations range from .40 to .80 (Strauss et al., 2006). In the MNB the NAART was used in conjunction with demographic data to estimate pre-morbid IQ (Meyers, 2013). Due to the role of this measure in determining estimated premorbid functioning, it was not included in the calculation of participant's OTBM or IIV.

Sentence Repetition.

SR is a 22-item test of verbal attention, expressive language, and receptive language in which patients repeat increasingly long sentences (Spreen & Strauss, 1991). Test-retest reliability after 1 year was .84, indicating that SR performance is generally stable over time (Klonoff et al., 1970). SR correlates highly with other tests of repetition, with correlation coefficients ranging from .75 to .88 (Lawriw, 1976; Shewan & Kertesz, 1980). SR correlates moderately with the Wechsler Memory Scale overall memory quotient (.38; Vargo & Black, 1984). Further, SR appears to be sensitive to left

hemisphere impairment (Meyers et al., 2000). As indicated in Table B.4, SR was part of the attention/working memory MNB domain (Meyers & Rohling, 2009).

Controlled Oral Word Association Test.

FAS is an assessment of word fluency and mental flexibility during which patients produce as many words as they can that begin with a specific letter in one minute (Spreen & Strauss, 1998). FAS consists of three trials with three different letters, typically F, A, and S. Internal consistency among F, A, and S and test-retest reliability is high, .83 and .74, respectively (Tombaugh et al., 1999). Correlations across different fluency tasks is high, with correlations ranging from .85 to .94 (Cohen & Stanczak, 2000; Lacy et al., 1996; Troyer, 2000). As indicated in Table B.4, FAS was part of the verbal reasoning/verbal comprehension MNB domain (Meyers & Rohling, 2009).

Animal Naming.

Animals is an assessment of word fluency and mental flexibility in which patients produce as many words as they can in one minute that are within a specific semantic cluster (i.e., animals; Spreen & Strauss, 1998). Correlations between semantic fluency tests with various target categories are moderately high, with correlations ranging from .66 to .71 (Delis et al., 2001; Riva et al., 2000). FAS generally correlates moderately with animals, with correlation coefficients ranging from .31 to .47, suggesting that each test provides reliable and unique variance (Johnson-Selfridge et al., 1998; Riva et al., 2000; Strauss et al., 2006; Tombaugh et al., 1999). Semantic fluency also correlates moderately to tests of naming, with correlation coefficients ranging from .57 to .68 (Strauss et al., 2006). As indicated in Table B.4, animals was part of the attention/working memory MNB domain (Meyers & Rohling, 2009).

Boston Naming Test.

The BNT is a 60-item measure of confrontation naming in which a patient generates the common name of objects displayed (Spreen & Strauss, 1998). If the patient misperceives an object, a semantic cue is given. If the patient generates the correct name at that point, they are still awarded full points for the item. Measures of internal consistency reliability of the BNT range from .78 to .96 (Strauss et al., 2006). Flanagan and Jackson (1997) demonstrated adequate reliability over one to two-week periods in older adults, with performances correlated at .91. BNT correlates highly with other measures of confrontation naming, such as the Multilingual Aphasia Examination Visual Naming Test (Axelrod et al., 1994; Schefft et al., 2003). As indicated in Table B.4, BNT was part of the verbal reasoning/verbal comprehension MNB domain (Meyers & Rohling, 2009).

Dichotic Listening.

DL is a 30-item test that involves listening to words produced in either the right or left ear or two words presented simultaneously in both ears and repeating the word(s) that were presented (Meyers et al., 2002; Roberts et al., 1994). This test measures both hemispheric speech dominance and central auditory processing via three index scores: left index, right index, and both ear index (Strauss et al., 2006). Test-retest reliability showed no significant differences in scores after six-weeks, suggesting adequate stability over time (Springer et al., 1991). DL scores are sensitive to both localized and diffuse brain injuries that affect the deep cerebral white matter pathways (Meyers et al., 2002; Roberts et al., 1994). As indicated in Table B.4, DL left and right index scores were part

of the verbal reasoning/verbal comprehension MNB domain, whereas the DL both ear index was part of the executive functioning MNB domain (Meyers & Rohling, 2009).

Auditory Verbal Learning Test.

The AVLT, or the Rey Auditory Verbal Learning Test, is a measure of verbal learning and memory, which assesses immediate recall memory, learning over trials, susceptibility to interference, delayed recall memory, and recognition memory for 15 target words (Spreen & Strauss, 1998). Internal reliability of the AVLT total score is .90 (Van den Burg & Kingma, 1999), whereas test-retest reliability ranged from .60 to .70 (Strauss et al., 2006). The AVLT delayed recall score correlates highly with the AVLT total score (Van den Burg & Kingma, 1999) suggesting strong construct validity. AVLT scores also correlate moderately well with other measures of learning and memory, suggesting that while the AVLT is similar to these other measures of learning and memory, it also provides reliable and unique variance compared to other measures (Crossen & Wiens, 1994; Johnstone et al., 2000; Stallings et al., 1995). This uniqueness may be derived from the non-contextualized nature of the word lists compared to other measures of list-learning memory and story memory. As indicated in Table B.4, AVLT trial 1 total was part of the attention/working memory MNB domain (Meyers & Rohling, 2009). AVLT learning, immediate recall, delayed recall, and recognition were all part of the verbal memory/auditory memory and learning MNB domain (Meyers & Rohling, 2009).

Rey Complex Figure Test.

The RCFT is a measure of visual-spatial construction and visual memory, which assesses perceptual organization in the copy, as well as immediate and delayed recall and

recognition for a non-verbal stimulus (Meyers & Meyers, 1995). Split-half reliability, computed for the details of the figure, are above .60 for the figure copy and above .80 for both immediate and delayed recall conditions (Berry et al., 1991; Fasteneau et al., 1996). This suggests that the details from the figure are fairly consistent with regards to their saliency and the underlying processes involved in their perception and recreation of the stimulus. Further, test-retest reliability ranges from .76 to .89 for immediate recall, delayed recall, and recognition scores (Meyers & Meyers, 1995).

Correlational and factor analytic studies support the validity of the RCFT as a measure of visual-spatial construction and memory (Strauss et al., 2006). For example, RCFT copy scores are only moderately correlated with immediate and delayed recall scores, coefficients of .33 and .38, respectively (Meyers & Meyers, 1995). Additionally, immediate and delayed recall scores are correlated at .88, yet recognition scores are correlated with recall at .15 (Meyers & Meyers, 1995). This suggests that recall and recognition memory as assessed with the RCFT, are two distinct aspects of memory. In terms of convergent and discriminant validity, RCFT scores are significantly related to other tasks of memory and construction ability but are not related to measures of language (Meyers & Meyers, 1995). As indicated in Table B.4, RCFT copy was part of the visual reasoning/perceptual organization domain (Meyers & Rohling, 2009), and RCFT immediate recall, delayed recall, and recognition performance scores were all part of the visual memory/nonverbal memory and learning MNB domain (Meyers & Rohling, 2009).

The Category Test- Victoria Revision.

VCT is an 81-item test measure of reasoning and problem solving which consists of deducing a classification principle by using feedback from the administrator (Spreen & Strauss, 1991). The original Category Test shows strong psychometric properties, such as internal consistency above .95 and moderate correlations with FSIQ and performance subtests of the Wechsler tests (Strauss et al., 2006). The VCT appears to preform similarly, as evidenced by cross-validation studies (Kozel & Meyers, 1998; Sherrill, 1985). As can be seen in Table B.4, VCT was part of the executive functioning MNB domain (Lezak et al., 2012; Strauss et al., 2006).

Forced Choice.

FC is a measure of attention in which a patient recalls as many items as they can from a list of 20 words presented verbally (Brandt et al., 1985). Subsequently, the patient chooses which word was on the 20-item list from pairs of words. This test differentiates amnesia malingering simulators, normal controls, and clinical groups, with individuals malingering amnesia performing significantly worse than individuals with organic amnesia on the forced-choice portion of this measure (Brandt et al., 1985). Similar measures of forced-choice performance validity measures have shown satisfactory internal consistency scores with malingered head injury simulators (Inman et al., 1998). Additionally, Arnett and Franzen (1997) found that the free-recall portion of a similar memory test correlates moderately to the Wechsler Memory Scale delayed recall index. This suggests that the free recall portion may indeed serve as a measure of impairment. As indicated in Table B.4, FC is part of the attention/working memory domain (Meyers & Rohling, 2009).

Imbedded Performance Validity.

In addition to performance scores on the above tests, nine imbedded measures of performance validity are calculated within the MNB. These validity measures are derived from FC, RCFT, JLO, TT, DLT, SR, AVLT recognition, FTT, and Block Design, Digit Span, and Digit Symbol/Coding from the WAIS III/IV (Meyers & Rohling, 2004; Meyers & Volbrecht, 2003). Each of the nine measure relies on patterns of performance that are statistically improbable. For example, inconsistent patterns of functioning or impairments within and across tests, unusually poor performances on specific "easy" items, and significantly more errors across tests than would be expected for given observed patient characteristics each factor into a person's performance on these validity scales. Failure on any one measure of performance validity is defined as follows: FC performance ≤ 10; attention, encoding, and storage memory error patterns (MEPs) in independently functioning individuals; Reliable Digit Span ≤ 6; JLO ≤ 12; TT Orientation ≤ 150; DLT ≤ 9; SR ≤ 9; AVLT recognition ≤ 9; or FTT speed > 10 points above an estimated FTT speed calculated based on Block Design, Digit Symbol/Coding, and the RCFT copy (Meyers & Rohling, 2004; see Meyers & Volbercht, 2003 for detailed explanations of each performance validity measure).

Procedure

Before the archival data was provided to the principal investigator, raw data were either normed using their respective manual (e.g., WAIS III/IV) and entered into the MNS, or they were entered into the MNS to be normed using a "smoothed" norming

system. Once standardized using the "smoothed" normative data, all standardized scores were converted to a common metric (T-scores) using the following formula:

$$T = \left(\left(\frac{ss - 10}{3}\right) * 10\right) + 50$$

where T is the normed ss minus the arbitrary mean used for ss, divided by the arbitrary *SD* of ss, multiplied by the arbitrary *SD* used for T-scores, and finally added to the arbitrary mean used for T-scores (Miller & Rohling, 2001). Data were then integrated into a modified Rohling Interpretive Method approach (RIM; Meyers, 2013).

The Rohling Interpretive Method

RMI (Miller & Rohling, 2001) provides a statistical method of evaluation and interpretation of standardized scores from flexible batteries that is similar to summaries provided through co-normed fixed batteries, such as the HII (Reitan & Wolfson, 1985). The basis of this methodology is derived from recommended practices for conducting meta-analytic reviews and allows for examination of performance at global, domain-specific, or test-specific levels (see Miller & Rohling, 2001 for the specific steps to using RIM).

This method of statistical evaluation and calculations of indices of neuropsychological performance minimizes common problems associated with cognitive assessment using flexible batteries, such as issues related to co-variation of instruments and weighting decision (Miller & Rohling, 2001). Additionally, the RIM within the MNS harnesses the statistical power associated with evaluating cognitive performance using multiple measures through calculated global (OTBM) and domain indices (Miller & Rohling, 2001), above and beyond that of any one measure used independently and

screening measures of cognitive functioning. These features, when used together, are thought to reduced Type II error and improve diagnostic accuracy. Thus, use of the modified RIM within the MNS may be particularly effective in detecting subtle deficits and strengths across and within cognitive domains.

Data Cleaning Procedures

Once test data were scored, normed, and integrated into a modified RIM approach, data were extracted from the MNS, deidentified, and provided to the principal investigator along with the neuropsychological report, if available. Necessary information, including demographic variables, such as age, sex, race, level of education, and occupation; current medications; substance use; psychiatric diagnoses; neurological diagnoses; medical diagnoses; and number of performance validity test failures were entered into a password protected database.

Each medication listed for study participants was assigned three classifications: (1) therapeutic use, (2) drug family, and (3) drug name (generic; See table B.2). While many medications can be used for various therapeutic uses, information that would aid in illuminating the intended therapeutic use of the prescription medication was not typically available. For example, medications were not associated with specific diagnoses. Additionally, information regarding dosage, duration of use, and frequency of use, as well as when the medication was last administered in relation to the neuropsychological testing session, which could impact their effects on cognition (Burchum & Rosenthal, 2016; Katzung, 2018), were not available in the data. Thus, all prescription medications reported by study participants were evaluated and the subsequent classifications were

based on their pharmaceutical composition, ACT code (WHO, 2021), and consultation with a pharmacology expert.

The levels of medication classification were hierarchical in nature, with therapeutic use being the largest classification. Each therapeutic use group generally contained several different drug classes. Each drug class generally contained several specific drug names. Drug names were the most specific identification of medications used in this study. Participants who denied use of any medications at the time of their neuropsychological evaluation were entered into a "no medication" group at each of the three classification levels and served as a control group for the analyses.

The number of medications reported at the time of the neuropsychological evaluation were used to categorize cases into three polypharmacy groups. Participants who reported using one to five medications at the time of their neuropsychological evaluation were assigned to the "no polypharmacy" group. Participants who reported using six or more medications at the time of their neuropsychological evaluation were assigned to the "polypharmacy" group. Participants who denied using any medications at the time of their neuropsychological evaluation were again assigned into the "no medication" group and served as a control group for the analyses.

Raw and standardized scores (T-scores corrected for age, education, gender, handedness, and ethnicity, where appropriate, according to MNS normative data or the WAIS III/IV manual) for all tests and MNB calculated domains were also entered into the database when available. If not already present in the archival data, OTBM, domain means, and IIV were calculated for each participant as follows.

Calculation of OTBM and Domain Means.

The OTBM and domain means were calculated for each participant with missing data based on the battery of tests administered to that patient and, if valid, standardized T-scores were available according to the modified RIM (see Miller & Rohling, 2001). Specifically, additional tests were assigned to the MNB domains described in Table B.4 with guidance from Miller and Rohling (2001), Lezak et al. (2012), and Strauss et al. (2006). Domain means were calculated by summing T-scores for a participant's cognitive performance across all scores within the domain and dividing by the number of data points available for that patient. The OTBM was calculated by summing T-scores for a participant's cognitive performance across all scores within the neuropsychological battery and dividing by the number of data points available for that patient.

Calculation of IIV.

If not already present in the archival data, IIV was calculated for each participant with valid, standardized data (T-scores) for performance measures of cognitive functioning according to the modified RIM (see Miller & Rohling, 2001). This was accomplished by taking the square root of the variance within one person's standardized score (T-score) performance on all MNB measures of cognitive function. The resulting overall test battery *SD* (OTBM *SD*) for each participant around their own OTBM serves as an index of variability within each participant's performance on measures across the test battery, IIV.

Plan of Analysis

To address Aim One, to evaluate the effects of medication use and polypharmacy on global cognitive functioning, as assessed by OTBM, a two-way ANCOVA was

planned. Similarly, a two-way ANCOVA was planned to address Aim Two and evaluate the effects of medication use and polypharmacy on global cognitive functioning, as assessed by IIV. To address Aim Three, two-way MANCOVAs were planned to evaluate the effects of medication use and polypharmacy on domain specific cognitive functioning.

Given the wide variety of medications reported by study participants, with some medications used by only one or two study participants, a deductive approach was taken to evaluate the effects of medication and polypharmacy on cognition using the medication classifications described above. For example, the initial evaluation of each aim was conducted using medications classified by therapeutic use. When a significant interaction or main effect was identified and subsequent simple effects/post-hoc analyses indicated that the OTBM, IIV, or cognitive domain means of subjects using medications from a specific therapeutic group differed significantly from subjects who were not taking medications from the therapeutic group and/or subjects who were not taking any medications, subsequent analyses were performed with the drug families categorized within the significant therapeutic use group.

Only drug families classified within the hierarchy of the therapeutic use categories which produced significant results were included in subsequent analyses. For those drug families, the same procedure was employed. Only when a significant interaction or main effect, and subsequent simple effects/post-hoc analyses, indicated that the OTBM, IIV, or cognitive domain mean of subjects using medications within the drug family was significantly different from subjects who were not taking medications from the drug family and/or subjects who were not taking any medications, were the drug

names within the medication group evaluated. Use of specific medications (medication name) were only included in analyses if both of the superordinate classifications were significant.

The rational for this deductive approach is twofold. First, use of this deductive approach aided in controlling family-wise error and the inflated risk of Type I error associated with completing multiple analyses. Second, by evaluating the superordinate medication category first (e.g., therapeutic use), we ensured that the analyses had the highest number of reported users, and therefore the highest possible power to find mean differences, before exploring the effects of medications with individual drug names. This later point was particularly important because there was significant variability across use of specific medications. For example, while many of the specific medications used by study participants fell into the same therapeutic use or drug family groups, many of the individual medications were only used by a few subjects each (e.g., < 5 subjects). Thus, if analyses were initially run with drug names, the extremely small sample sizes across drug names would not have had sufficient power to identify significant results.

A Priori Power Analysis

Another way power was optimized in this study was by limiting analyses to groups with a sufficient number of medication users. To determine the optimal sample size for the primary analyses, an a priori power analysis was conducted using G*Power (Faul et al., 2008) anticipating a medium effect size and a Bonferroni alpha correcting for 10 analyses. Results from this analysis indicated that a sample size of 476 was required to achieve a power of .80 given an effect size of .20 (medium effect size), a Bonferroni corrected alpha of .005, and a numerator *df* of 4, for 7 groups, with covariates. Therefore,

the sample size of 497 was determined to be sufficiently powered to carry out the primary analyses. However, considering this overall sample size across groups, medication use categories needed at least 68 subjects to adequately power the analysis. Therefore, medication use categories with less than 68 subjects were not evaluated.

CHAPTER V

RESULTS

Preliminary Analyses

Prior to conducting the primary analyses, all variables were assessed for coding errors, missing values, univariate and multivariate outliers, and assumptions of normality using SPSS, Version 28 (IBM Corp., 2021). Coding errors were corrected based on the available raw scores and T-scores. Coding errors that were unable to be corrected were coded as missing.

With regard to missing data, for the 497 cases, the proportion of missing data was minimal across most study variables. Data were missing across these variables as follows: diagnosis (19.5%); medication (0%); polypharmacy (0%); premorbid estimate (2.4%); OTBM (0%); IIV (4.4%); Attention and Working Memory (0.6%); Processing Speed (0.8%); Verbal Reasoning (0.4%); Visual Reasoning (0.2%); Verbal Memory (1.4%), Visual Memory (3.2%); Executive Functioning (0%); Dominant Motor Functioning (6.8%); and Non-Dominant Motor Functioning (7.0%). Analyses of these variables indicated that 49 subjects (9.9%) were missing data on any one variable.

A series of one-way ANOVAs indicated that cases with missing values were systematically related to the sequence of data entry (a randomly constructed variable), the neuropsychologist who evaluated the patient, total PVT failures, processing speed, and executive functioning. This pattern of missingness is consistent with data that is missing

at random (MAR). While it is possible that the pattern of missingness is systematically related to another variable not measured in the data set, indicating that the data is not missing at random (NMAR), there is no obvious theoretical reason to suspect this in the present data.

Given that cases with missing data were minimal across most variables, in most instances constituting less than 5% of the total sample, and the data are likely MAR, participants with missing data were retained in the sample. Subsequent analyses were completed on the sample of 497 cases. Pairwise deletion was used to address the minimal amount of missing data in primary analyses (Schlomer et al., 2010).

Univariate outliers, defined as observations having z-scores > |3|, were found for 3 cases (0.6%) on premorbid estimate, 6 cases (1.2%) on IIV, 2 cases (0.4%) on processing speed, 7 cases (1.4%) on verbal reasoning, 1 case (0.2%) on visual reasoning, 1 case on executive functioning (0.2%), 8 cases (1.6%) on dominant motor functioning, and 4 cases (0.8%) on non-dominant motor functioning. Of these, only one value, on non-dominant motor functioning, was extreme in nature (e.g., z-score > 5.0) and was replaced with the next closest value. Mahalanobis distances greater than 32.91 was identified for 10 cases (2%), suggesting they may be possible multivariate outliers. Given the relatively small percentage of possible univariate and multivariate outliers, the relatively large sample size, and the fact that only one univariate outlier was extreme in magnitude requiring replacement, no other cases were deleted or modified, as recommended by Meyers et al. (2017).

With regard to the distributions of variables, IIV and dominant motor functioning exhibited slight deviations from normality as evidenced by skew and kurtosis values, and

visual inspection of Q-Q plots and histograms. Specifically, IIV was slightly positively skewed (1.09) and dominant motor functioning was slightly negatively skewed (-1.37). Distributions for both IIV and dominant motor functioning were leptokurtic (kurtosis = 1.62 and 3.53, respectively). However, according to Kim (2013), these values do not represent substantial deviations from normality given the large sample size. Distributions of all other variables were within normal limits with regard to skewness, kurtosis, and visual examination of QQ-plots and histograms. Therefore, no data transformations were deemed necessary. Linearity assumptions were deemed satisfactory by visual inspection of bivariate scatterplots and significant bivariate correlations (see Tables B.5 through B.11 for correlations between study variables).

Given that only two variables showed slight deviations from normality and simulation analyses indicate that ANOVA modes are robust to deviations from non-normality, particularly in larger samples (Khan & Rayner, 2003), the data were judged to be appropriate for further analyses of variance. However, due to sample size limitations only medications within the following therapeutic use categories were able to be evaluated in the primary analyses: anticholinergics, antidepressants, anxiolytics, analgesics, antiepileptics, cardiovascular, anti-inflammatory, and hormones using the deductive approach described above. Given the reduction in analyses performed, the Bonferroni corrected alpha value was adjusted accordingly.

Additionally, given the significant relationships identified across the outcome variables, medication's therapeutic use categories, diagnoses, and additional cognitive and demographic related variables (e.g., estimated premorbid functioning, age, location of evaluation), as can be seen in tables B.5 through B.11, these variables were evaluated

for potential use as covariates in the primary analyses. Estimated premorbid functioning, subject age, location of evaluation; use of antidepressants, anxiolytics, antipsychotics, analgesics, AEDs, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, severe mental illness (SMI), learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain conformed to the assumptions of linearity of regression and homogeneity of regression at both the univariate and the multivariate levels. Therefore, these variables were used as covariates in all primary analyses, except for when the corresponding or subordinate medication variable was used as an independent variable.

Primary Analyses Aims One and Two

To examine the effects of medication use and polypharmacy on global cognitive functioning, as assessed by OTBM and IIV, (use of medication) X 3 (polypharmacy) between subjects ANCOVAs were used to determine if there was an interaction between medication use and polypharmacy level on OTBM or IIV, if there were differential effects of medication use on the OTBM or IIV, and if there were differential effects of levels of polypharmacy on OTBM or IIV. See tables C.1-C.20 in Appendices for detailed results for Aims One and Two, as analyzed by two-way ANCOVA on global cognition as measured by the OTBM and IIV, respectively.

Anticholinergic Medications

To address Aim One, a 3 (use of anticholinergic medication) X 3 (polypharmacy) between subjects ANCOVA evaluated the interaction and main effects of the use of

anticholinergic medication and polypharmacy on the OTBM. Levene's test was not statistically significant, $F(4, 383) = 2.40$ $p = .05$. Therefore, the data did not violate the assumption of homogeneity of variance, and it was deemed appropriate for further analysis.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1, 364) = 27.10$, $p < .001$], estimated premorbid functioning [$F(1, 364) = 167.38$ $p < .001$], neurocognitive disorder [$F(1, 364) = 15.94$, $p < .001$], moderate to severe TBI [$F(1, 364) = 13.18$, $p < .001$], and cardiovascular diagnoses [$F(1, 364) = 21.622$, $p < .001$] were statistically significant. However, there was not a statistically significant interaction between the effects of using anticholinergic medication and polypharmacy, $F(1, 364) = 3.65$, $p = .05$, nor were there significant main effects of use of anticholinergic medications, $F(1, 364) = 0.45$, $p = .50$, or polypharmacy, $F(1, 364) = .25$, $p = .61$, on OTBM. Therefore, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no interaction between the use of anticholinergic medication and polypharmacy on overall cognitive functioning as assessed by the OTBM. There also were not independent effects of use of anticholinergic medications or polypharmacy on overall cognitive functioning as assessed by the OTBM.

To address Aim Two, a 3 (use of anticholinergic medication) X 3 (polypharmacy) between subjects ANCOVA evaluated the interaction and main effects of the use of anticholinergic medication and polypharmacy on IIV. Levene's test was not statistically significant, $F(4, 373) = 1.62$, $p = .17$. Therefore, the data did not violate the assumption of homogeneity of variance, and it was deemed appropriate for further analysis.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1, 354) = 45.03$, $p < .001$], moderate to severe TBI [$F(1, 354) = 8.85$, $p = .003$], and cardiovascular diagnoses [$F(1, 354) = 15.33$, $p < .001$] were statistically significant. There was not a statistically significant interaction between the effects of using anticholinergic medication and polypharmacy, $F(1, 354) = 3.82$, $p = .05$. There were also no significant main effects of use of anticholinergic medications, $F(1, 354) = 0.65$, $p = .42$ or polypharmacy on IIV, $F(1, 354) = 0.88$, $p = .35$. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no interaction between use of anticholinergic medications and polypharmacy on overall cognitive functioning as assessed by IIV. There also were not independent effects of use of anticholinergic medications or polypharmacy on overall cognitive functioning as assessed by IIV.

Antidepressant Medications

To address Aim One, a 3 (use of antidepressant) X 3 (polypharmacy) between subjects ANCOVA evaluated the interaction and main effects of the use of antidepressant medication and polypharmacy on the OTBM. Levene's test was not statistically significant, $F(4, 383) = 1.69$, $p = .15$, indicating that the data did not violate the assumption of homogeneity of variance. Therefore, the data was deemed appropriate for further analyses of variance.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1, 363) = 23.93$, $p < .001$], estimated premorbid functioning [$F(1, 363) = 160.82$, $p < .001$], neurocognitive disorder diagnosis [$F(1, 363) = 16.89$, $p < .001$], moderate to

severe TBI [$F(1, 363) = 14.94$, $p < .001$], and cardiovascular diagnoses [$F(1, 363) = 22.07$, $p < .001$] were statistically significant. There was not a statistically significant interaction between the effects of using antidepressant medication and polypharmacy, $F(1, 363) = 0.09$, $p = .77$, nor were there significant main effects for the use of antidepressant medications, $F(1, 363) = 0.80$, $p = .37$ on OTBM, or polypharmacy on OTBM, $F(1, 363) = .04$, $p = .85$. Therefore, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no interaction between use of antidepressant medications and polypharmacy on overall cognitive functioning as assessed by the OTBM. There also were not independent effects of use of antidepressant medications or polypharmacy on overall cognitive functioning as assessed by the OTBM.

To address Aim Two, a 3 (use of antidepressant) X 3 (polypharmacy) between subjects ANCOVA evaluated the interaction and main effects of the use of antidepressant medication and polypharmacy on IIV. Levene's test was not statistically significant, $F(4, 373) = 1.10$, $p = .36$, indicating that the data did not violate the assumption of homogeneity of variance. Therefore, the data was deemed appropriate for further analyses of variance.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1,353) = 24.37$, $p < .001$), use of analgesics [$F(1,353) = 8.50$, $p = .004$], moderate to severe TBI [$F(1,353) = 11.83$, $p < .001$], and cardiovascular diagnoses [$F(1,353) = 16.53$, $p < .001$] were statistically significant. There was not a statistically significant interaction between the effects of using antidepressant medication and polypharmacy, $F(1, 353) = 0.01$, $p = .93$, nor was there significant main effect of use of antidepressant medications,

$F(1, 353) = 0.18$, $p = .68$ on IIV. There was a significant main effect of polypharmacy on IIV at the .05 alpha level, $F(1, 353) = 5.29$, $p = .02$. However, when the more stringent alpha level of .006 (.05/8) was employed to reduce the risk of Type I error, this main effect was no longer considered significant. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no significant interaction between the use of antidepressant medication and polypharmacy on overall cognitive functioning, as assessed by IIV. There also were not significant independent effects of use of antidepressant medications or polypharmacy on overall cognitive functioning as assessed by IIV at the alpha level of .006.

Anxiolytic Medications

To address Aim One, a 3 (use of anxiolytics) X 3 (polypharmacy) between subjects ANCOVA evaluated the interaction and main effects of the use of anxiolytic medication and polypharmacy on the OTBM. Levene's test was statistically significant, $F(4, 383) = 3.29$, $p = .01$, indicating that the data violated the assumption of homogeneity of variance. Therefore, a more stringent alpha value was used when determining whether the univariate tests were statistically significant. Given that a Bonferroni corrected alpha of .006 was employed due to the large number of statistical analyses being conducted, an alpha value of .001 was used for this analysis to further reduce the risk of Type I error.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1, 362) = 25.66$, $p < .001$], estimated premorbid functioning [$F(1, 362) = 162.02$, $p < .001$], use of anti-inflammatory medications [$F(1, 362) = 4.34$, $p = 0.04$], neurocognitive disorder diagnosis [$F(1, 362) = 17.02$, $p < .001$], moderate to severe TBI [$F(1, 362) =$

13.90, $p < .001$], cardiovascular diagnoses [$F(1, 362) = 25.41$, $p < .001$], and respiratory diagnoses [$F(1, 362) = 4.17$, $p = .04$] were statistically significant. There was a statistically significant interaction between the effects of using anxiolytic medications and polypharmacy, $F(1, 362) = 6.48$, $p = .01$. However, when the more stringent corrected alpha of .001 is used, this interaction is not considered statistically significant. Neither the main effects for the use of anxiolytic medications, $F(1, 362) = 2.00$, $p = .16$, nor polypharmacy, $F(1, 362) = .03$, $p = .88$, on OTBM were statistically significant. Therefore, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no significant interaction between use of anxiolytic medications and polypharmacy on overall cognitive functioning as assessed by the OTBM at the Bonferroni corrected alpha value of .001. There also were not significant independent effects of use of anxiolytic medications or polypharmacy on overall cognitive functioning as assessed by the OTBM at the Bonferroni corrected alpha value of .001.

To address Aim Two, a 3 (use of anxiolytics) X 3 (polypharmacy) between subjects ANCOVAs evaluated the interaction and main effects of the use of anxiolytic medication and polypharmacy on IIV. Levene's test was not statistically significant, $F(4, 373) = 1.21$, $p = .31$, indicating that the data did not violate the assumption of homogeneity of variance. Therefore, the data was deemed appropriate for further analyses of variance.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1,352) = 44.49$, $p < .001$], use of analgesics [$F(1,352) = 7.09$, $p = .008$], diagnosis of a

neurodevelopmental disorder [$F(1, 352) = 4.08$, $p = .04$], moderate to severe TBI [$F(1, 352) = 9.85$, $p = .002$], and cardiovascular diagnoses [$F(1, 352) = 18.80$, $p < .001$] were statistically significant. There was a statistically significant interaction between the effects of using anxiolytic medication and polypharmacy, $F(1, 352) = 4.76$, $p = .03$. However, when a more stringent corrected alpha of .006 is used, this interaction is not considered statistically significant. Similarly, there was a significant main effect of polypharmacy on IIV, $F(1, 352) = 4.47$, $p = .04$, but when compared to the more stringent alpha of .006, this main effect was no longer significant. No main effect of use of anxiolytic medication was identified, $F(1, 352) = 1.79$, $p = .18$. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no interaction between anxiolytic medication use and polypharmacy on overall cognitive functioning as assessed by IIV at $p < .006$. There also were not independent effects of use of anxiolytic medications or polypharmacy on overall cognitive functioning as assessed by IIV at the alpha level of .006.

Analgesic Medications

To address Aim One, a 3 (use of analgesics) X 3 (polypharmacy) between subjects ANCOVA evaluated the interaction and main effects of the use of analgesic medication and polypharmacy on the OTBM. Levene's test was statistically significant, $F(4, 383) = 2.59$, $p = .04$, indicating that the data violated the assumption of homogeneity of variance. Therefore, a more stringent alpha value was used when determining whether the univariate tests were statistically significant. Given that a Bonferroni corrected alpha

of .006 was employed due to the large number of statistical analyses conducted, an alpha value of .001 was used for this analysis to further reduce the risk of Type I error.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1, 362) = 25.13$, $p < .001$], estimated premorbid functioning [$F(1, 362) = 157.84$, $p < .001$], neurocognitive disorder diagnosis [$F(1, 362) = 15.00$, $p < .001$], moderate to severe TBI [$F(1, 362) = 14.35$, $p < .001$], and cardiovascular diagnoses [$F(1, 362) = 22.70$, $p < .001$] were statistically significant. The interaction between the effects of using analgesic medications and polypharmacy was not significant, $F(1, 362) = 2.00$, $p = .16$. The main effect of polypharmacy on the OTBM also was not significant, $F(1, 362) = 0.01$, $p = .93$. The main effect for the use of analgesic medications was significant at the .05 alpha level, $F(1, 362) = 3.97$, $p < .05$. However, when the main effect of use of analgesic medications was compared to the more stringent alpha of .001, the effect was no longer significant. Therefore, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no interaction between analgesic medication use and polypharmacy on overall cognitive functioning as assessed by the OTBM at the alpha value of .001. There also were not independent effects of analgesic medication use or polypharmacy on overall cognitive functioning as assessed by the OTBM at the alpha value of .001.

To address Aim Two, a 3 (use of analgesics) X 3 (polypharmacy) between subjects ANCOVA evaluated the interaction and main effects of the use of analgesic medication and polypharmacy on IIV. Levene's test was not statistically significant, $F(4, 373) = 1.59$, $p = .18$, indicating that the data did not violate the assumption of

homogeneity of variance. Therefore, the data was deemed appropriate for further analyses of variance.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1,352) = 45.89$, $p < .001$], moderate to severe TBI [$F(1, 352) = 10.25$, $p = .001$], and cardiovascular diagnoses [$F(1, 352) = 16.58$, $p < .001$] were statistically significant. The interaction between the effects of using analgesic medication and polypharmacy was not significant, $F(1, 352) = 2.89$, $p = .09$. However, both the main effect of analgesic medication use and the main effect of polypharmacy on IIV were significant, $F(1, 352) = 11.29$, $p = < .001$, $\eta^2 = .02$, and $F(1, 352) = 4.65$, $p = .03$, respectively. Only the main effect of analgesic medication on IIV remained significant when applying the more stringent Bonferroni corrected alpha of .006. This result indicates that subjects taking analgesic medications showed more cognitive variability ($M = 10.51$, SD = 2.72) than those not taking analgesic medication ($M = 9.99$, SD = 2.37) and those not taking any prescription medications ($M = 9.43$, SD = 2.73).

Analgesic Drug Families.

Triptans. Given this finding, and to further evaluate Aim Two with regard to analgesic medication families, four subsequent 3 (Analgesic group) X 3 (polypharmacy) between subjects ANCOVAs were used to evaluate the interaction and main effects of the use of medication in analgesic families and polypharmacy on IIV. The first two-way ANCOVA evaluated the interaction and main effects of the use of triptans and polypharmacy on IIV. Levene's test was not statistically significant, $F(4, 373) = 1.72$, $p = .15$, indicating that the data did not violate the assumption of homogeneity of variance. Therefore, the data was deemed appropriate for further analyses of variance.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1, 352) = 44.03$, $p < .001$], neurocognitive disorders [$F(1, 352) = 3.98$, $p = .05$], moderate to severe TBI [$F(1, 352) = 9.78$, $p = .002$], and cardiovascular diagnoses [$F(1, 352) = 17.47$, $p < .001$] were statistically significant. The interaction between the effects of using triptans and polypharmacy was not significant, $F(1, 352) = 0.44$, $p = .51$. Additionally, the main effect of polypharmacy on IIV was not significant, $F(1, 352) = 2.79$, $p = .10$. However, the main effect of triptan use on IIV was significant, $F(1, 352) = 12.91$, $p = < .001$, $\eta^2 = .03$. This result indicates that subjects using triptan medications showed more cognitive variability ($M = 13.08$, SD = 3.96) than those not taking analgesic medication ($M = 9.24$, SD = 2.40) and those not taking any prescription medications ($M = 9.26$, SD = 2.73).

This significant difference between subjects using triptan medications and subjects who do not use triptan medications suggests that further exploration with regard to specific drug names is warranted. However, these analyses were unable to be conducted due to the significantly low frequencies of almotriptan, eletriptan, rizatriptan, and sumatriptan use in the sample. Specifically, only one participant each reported using almotriptan and eletriptan, and two participants each reported using rizatriptan and sumatriptan.

Opioids. The next two-way ANCOVA evaluated the interaction and main effects of the use of opioids and polypharmacy on IIV. Levene's test was not statistically significant, $F(4, 373) = 2.32$, $p = .06$, indicating that the data did not violate the assumption of homogeneity of variance. Therefore, the data was deemed appropriate for further analyses of variance.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1, 352) = 44.03$, $p < .001$], neurocognitive disorders [$F(1, 352) = 4.42$, $p = .04$], moderate to severe TBI [$F(1, 352) = 8.85$, $p = .003$], and cardiovascular diagnoses [$F(1, 352) = 15.70$, $p < .001$] were statistically significant. There was not a statistically significant interaction between the effects of using opioid medication and polypharmacy, $F(1, 352) = 0.07$, $p = .80$, nor were there significant main effects of the use of opioids, $F(1, 352) = 0.10$, $p = .75$, or polypharmacy on IIV, $F(1, 352) = 0.10$, $p = .75$. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no interaction between opioid medication use and polypharmacy on overall cognitive functioning as assessed by IIV at the Bonferroni corrected alpha value of .006. There also were not independent effects of the use of opioid medications or polypharmacy on overall cognitive functioning as assessed by IIV at the Bonferroni corrected alpha value of .006.

Opioid Combinations. The next two-way ANCOVA evaluated the interaction and main effects of the use of opioid combination medications and polypharmacy on IIV. Levene's test was not statistically significant, $F(4, 373) = 1.65$, $p = .16$, indicating that the data did not violate the assumption of homogeneity of variance. Therefore, the data was deemed appropriate for further analyses of variance.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1, 352) = 42.94$, $p < .001$], neurocognitive disorders [$F(1, 352) = 4.42$, $p = .04$], moderate to severe TBI [$F(1, 352) = 9.20$, $p = .003$], and cardiovascular diagnoses [$F(1, 352) = 15.49$, $p < .001$] were statistically significant. There was not a statistically

significant interaction between the effects of using opioid combination medications and polypharmacy, $F(1, 352) < 0.01$, $p = .98$, nor were there significant main effects of opioid combination use, $F(1, 352) = 2.13$, $p = .15$, or polypharmacy on IIV, $F(1, 352) = 1.70$, $p = .19$. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no effect of opioid combination medication use, polypharmacy, or the interaction between the two, on overall cognitive functioning as assessed by IIV at the Bonferroni corrected alpha value of .006.

Non-Opioid Analgesics. The final two-way ANCOVA within the analgesic family analyses evaluated the interaction and main effects of the use of non-opioid analgesics and polypharmacy on IIV. Levene's test was statistically significant, $F(4, 373) = 3.57$, $p = .007$, indicating that the data violated the assumption of homogeneity of variance. Therefore, a more stringent alpha value was used when determining whether the univariate tests were statistically significant. Given that a Bonferroni corrected alpha of .006 was employed due to the large number of statistical analyses conducted, an alpha value of .001 was used for this analysis to further reduce the risk of Type I error.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1, 352) = 45.07$, $p < .001$], moderate to severe TBI [$F(1, 352 = 9.17$, $p = .003$], and cardiovascular diagnoses [$F(1, 352) = 14.73$, $p < .001$] were statistically significant. There was not a statistically significant interaction between the effects of using non-opioid analgesics and polypharmacy, $F(1, 352) < 0.01$, $p = .98$, nor were there significant main effects of non-opioid analgesic use, $F(1, 352) = 0.20$, $p = .65$, nor polypharmacy on IIV, $F(1, 352) = 0.01$, $p = .93$. Overall, despite adjusting for relevant variables, such as

the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no interaction between use of opioid combination medications and polypharmacy on overall cognitive functioning as assessed by IIV at the corrected alpha value of .001. There also were not independent effects of opioid combination medication use or polypharmacy on overall cognitive functioning as assessed by IIV at the corrected alpha value of .001.

Antiepileptic Medications

To address Aim One, a 3 (use of antiepileptics) X 3 (polypharmacy) between subjects ANCOVA evaluated the interaction and main effects of the use of antiepileptic medication and polypharmacy on the OTBM. Levene's test was not statistically significant, $F(4, 383) = 1.55$, $p = .19$, indicating that the data did not violate the assumption of homogeneity of variance. Therefore, the data was deemed appropriate for further analyses of variance.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1, 362) = 24.90$, $p < .001$], estimated premorbid functioning [$F(1, 362) = 155.96$, $p < .001$], use of anti-inflammatory medications [$F(1, 362) = 5.09$, $p = 0.03$], neurocognitive disorder diagnosis [$F(1, 362) = 14.75$, $p < .001$], moderate to severe TBI [$F(1, 362) = 12.613$, $p < .001$], and cardiovascular diagnoses [$F(1, 362) = 21.84$, $p < .001$] were statistically significant. There was a statistically significant interaction between the effects of using antiepileptic medications and polypharmacy, $F(1, 362) = 4.51$, $p = .03$. However, when the more stringent corrected alpha of .006 is used, this interaction is not considered statistically significant. Neither the main effects for the use of antiepileptic medications, $F(1, 362) = 3.41$, $p = .07$, nor polypharmacy, $F(1, 362) = 0.88$, $p = .35$, on

OTBM were statistically significant. Therefore, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no interaction between use of antiepileptic medication and polypharmacy on overall cognitive functioning as assessed by the OTBM at the Bonferroni corrected alpha value of .006. There also were not independent effects of the use of antiepileptic medications or polypharmacy on overall cognitive functioning as assessed by the OTBM.

To address Aim Two, a 3 (use of antiepileptics) X 3 (polypharmacy) between subjects ANCOVA evaluated the interaction and main effects of the use of antiepileptic medications and polypharmacy on IIV. Levene's test was not statistically significant, $F(4, 373) = 0.99$, $p = .42$, indicating that the data did not violate the assumption of homogeneity of variance. Therefore, the data was deemed appropriate for further analyses of variance.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1,352) = 44.51$, $p < .001$], use of analgesics [$F(1,352) = 9.27$, $p = .003$], moderate to severe TBI [$F(1, 352) = 8.83$, $p = .003$], and cardiovascular diagnoses [$F(1, 352) = 16.46$, $p < .001$] were statistically significant. There was a statistically significant interaction between the effects of using antiepileptic medication and polypharmacy, $F(1, 352) = 4.79$, $p = .03$. However, when a more stringent corrected alpha of .006 was used, this interaction was no longer considered statistically significant. Similarly, there was a significant main effect of polypharmacy on IIV, $F(1, 352) = 9.56$, $p = .002$, $\eta^2 = .20$. Although, this significant main effect remained, even when compared to a more conservative alpha of .006. No main effect of use of antiepileptic medication on IIV was

identified, $F(1, 352) = 1.87$, $p = .17$. These results indicate that subjects without polypharmacy showed more cognitive variability ($M = 10.45$, SD = 2.42) than those taking more than 5 medications (e.g., polypharmacy; $M = 8.89$, SD = 2.52) and those not taking any prescription medications ($M = 7.78$, SD = 2.73).

Cardiovascular Medications

To address Aim One, a 3 (cardiovascular medications) X 3 (polypharmacy) between subjects ANCOVA evaluated the interaction and main effects of the use of cardiovascular medications and polypharmacy on OTBM. Levene's test was not statistically significant, $F(4, 383) = 1.57$, $p = .18$, indicating that the data did not violate the assumption of homogeneity of variance. Therefore, the data was deemed appropriate for further analyses of variance.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1, 362) = 23.28$, $p < .001$], estimated premorbid functioning [$F(1, 362) = 158.11$, $p < .001$], use of anti-inflammatory medications [$F(1, 362) = 3.97$, $p < 0.05$], neurocognitive disorder diagnosis [$F(1, 362) = 16.81$, $p < .001$], moderate to severe TBI [$F(1, 362) = 14.14$, $p < .001$], and cardiovascular diagnoses [$F(1, 362) = 22.14$, $p < .001$] were statistically significant. The interaction between the effects of using cardiovascular medications and polypharmacy was not significant, $F(1, 362) = 0.53$, $p = .47$. Additionally, neither the main effects of cardiovascular medication use, $F(1, 362) = 2.48$, $p = .12$, nor polypharmacy, $F(1, 362) = 0.13$, $p = .72$, on OTBM were statistically significant. Therefore, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no interaction between use of

cardiovascular medication and polypharmacy on overall cognitive functioning as assessed by the OTBM at the Bonferroni corrected alpha value of .006. There also were not independent effects of cardiovascular medication use or polypharmacy on overall cognitive functioning as assessed by the OTBM at the Bonferroni corrected alpha value of .006.

To address Aim Two, a 3 (use of antiepileptics) X 3 (polypharmacy) between subjects ANCOVA evaluated the interaction and main effects of the use of cardiovascular medications and polypharmacy on IIV. Levene's test was not statistically significant, $F(4, 373) = 2.08$, $p = .08$, indicating that the data did not violate the assumption of homogeneity of variance. Therefore, the data was deemed appropriate for further analyses of variance.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1,352) = 43.88$, $p < .001$], use of analgesics [$F(1,352) = 8.44$, $p = .004$], moderate to severe TBI [$F(1, 352) = 9.95$, $p = .002$], and cardiovascular diagnoses [$F(1, 352) = 16.13$, $p < .001$] were statistically significant. The interaction between the effects of using cardiovascular medication and polypharmacy was not significant, $F(1, 352) = 0.23$, $p = .63$. No main effect of use of cardiovascular medication on IIV was identified, $F(1, 352) = 0.01$, $p = .91$. There was a significant main effect of polypharmacy on IIV, $F(1, 352) = 6.76$, $p = .01$. However, when the more stringent corrected alpha of .006 was used, this interaction was no longer considered statistically significant. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no interaction between use of cardiovascular medication and polypharmacy on overall

cognitive functioning as assessed by IIV at the Bonferroni corrected alpha value of .006. There also were not independent effects of cardiovascular medication use or polypharmacy on overall cognitive functioning as assessed by IIV at the Bonferroni corrected alpha value of .006.

Anti-Inflammatory Medications

To address Aim One, a 3 (anti-inflammatory medication use) X 3 (polypharmacy) between subjects ANCOVA evaluated the interaction and main effects of the use of anti-inflammatory medications and polypharmacy on the OTBM. Levene's test was not statistically significant, $F(4, 383) = 1.83$, $p = .18$, indicating that the data did not violate the assumption of homogeneity of variance. Therefore, the data was deemed appropriate for further analyses of variance.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1, 362) = 24.03$, $p < .001$], estimated premorbid functioning [$F(1, 362) = 157.59$, $p < .001$], neurocognitive disorder diagnosis [$F(1, 362) = 16.76$, $p < .001$], moderate to severe TBI [$F(1, 362) = 14.08$, $p < .001$], and cardiovascular diagnoses [$F(1, 362) = 21.99$, $p < .001$] were statistically significant. The interaction between the effects of using anti-inflammatory medications and polypharmacy was not significant, $F(1, 362) = 0.03$, $p = .87$. Additionally, neither the main effects for the use of anti-inflammatory medications, $F(1, 362) = 3.19$, $p = .08$, nor polypharmacy, $F(1, 362) = 0.18$, $p = .68$, on OTBM were statistically significant. Therefore, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no interaction between anti-inflammatory medication use and polypharmacy on overall cognitive functioning as assessed by the

OTBM. There also were not independent effects of anti-inflammatory medication use or polypharmacy on overall cognitive functioning as assessed by the OTBM.

To address Aim Two, a 3 (use of anti-inflammatory) X 3 (polypharmacy) between subjects ANCOVA evaluated the interaction and main effects of the use of anti-inflammatory medications and polypharmacy on IIV. Levene's test was not statistically significant, $F(4, 373) = 1.38$, $p = .24$, indicating that the data did not violate the assumption of homogeneity of variance. Therefore, the data was deemed appropriate for further analyses of variance.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1,352) = 43.68$, $p < .001$], use of analgesics [$F(1,352) = 8.75$, $p = .003$], moderate to severe TBI [$F(1, 352) = 9.78$, $p = .002$], and cardiovascular diagnoses [$F(1, 352) = 16.05$, $p < .001$] were statistically significant. The interaction between the effects of using anti-inflammatory medication and polypharmacy was not significant, $F(1, 352) = 0.29$, $p = .59$. No main effect of use of anti-inflammatory medication on IIV was identified, $F(1, 352) = 0.34$, $p = .56$. There was a significant main effect of polypharmacy on IIV, $F(1, 352) = 5.77$, $p = .02$. However, when the more stringent corrected alpha of .006 was used, this interaction was no longer considered statistically significant. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no interaction between anti-inflammatory medication use and polypharmacy on overall cognitive functioning as assessed by IIV. There also were not independent effects of anti-inflammatory medication use or polypharmacy on overall cognitive functioning as assessed by IIV at the Bonferroni corrected alpha value of .006.

Hormone Medications

To address Aim One, a 3 (hormone medication use) X 3 (polypharmacy) between subjects ANCOVA evaluated the interaction and main effects of the use of hormone medications and polypharmacy on the OTBM. Levene's test was not statistically significant, $F(4, 383) = 1.68$, $p = .15$, indicating that the data did not violate the assumption of homogeneity of variance. Therefore, the data was deemed appropriate for further analyses of variance.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1, 362) = 24.20$, $p < .001$], estimated premorbid functioning [$F(1, 362) = 157.55$, $p < .001$], neurocognitive disorder diagnosis [$F(1, 362) = 16.75$, $p < .001$], moderate to severe TBI [$F(1, 362) = 14.20$, $p < .001$], and cardiovascular diagnoses [$F(1, 362) = 22.12$, $p < .001$] were statistically significant. The interaction between the effects of using hormone medications and polypharmacy was not significant, $F(1, 362) = 0.23$, $p = .63$. Additionally, neither the main effects for the use of hormone medications, $F(1, 362) = 0.09$, $p = .77$, nor polypharmacy, $F(1, 362) = 0.26$, $p = .61$, on OTBM were statistically significant. Therefore, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no interaction between use of hormone medications and polypharmacy on overall cognitive functioning as assessed by the OTBM. There also were not independent effects of hormone medication use and polypharmacy on overall cognitive functioning as assessed by the OTBM.

To address Aim Two, a 3 (use of hormones) X 3 (polypharmacy) between subjects ANCOVA evaluated the interaction and main effects of the use of hormone

medications and polypharmacy on IIV. Levene's test was not statistically significant, $F(4, 373) = 1.00$, $p = .41$, indicating that the data did not violate the assumption of homogeneity of variance. Therefore, the data was deemed appropriate for further analyses of variance.

In the omnibus analysis, the covariate effects of the location of the evaluation [$F(1,352) = 43.90$, $p < .001$], use of analgesics [$F(1,352) = 8.27$, $p = .004$], moderate to severe TBI [$F(1, 352) = 10.12$, $p = .002$], and cardiovascular diagnoses [$F(1, 352) = 16.37$, $p < .001$] were statistically significant. The interaction between the effects of using hormone medications and polypharmacy was not significant, $F(1, 352) = 0.18$, $p = .67$. No main effect of use of hormones on IIV was identified, $F(1, 352) = 1.13$, $p = .29$. There was a significant main effect of polypharmacy on IIV, $F(1, 352) = 6.76$, $p = .01$. However, when the more stringent corrected alpha of .006 was used, this interaction was no longer considered statistically significant. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no interaction between use of hormone medications and polypharmacy on overall cognitive functioning as assessed by IIV. There also were not independent effects of hormone medication use and polypharmacy on overall cognitive functioning as assessed by IIV at the Bonferroni corrected alpha value of .006.

Primary Analyses Aim Three

To examine the effects of medication use and polypharmacy on domain-specific cognitive functioning, two-way MANCOVAs were used to evaluate the interactions and

main effects of medication use and polypharmacy on the following cognitive domain means: attention/working memory, processing speed, verbal reasoning, visual reasoning, verbal memory, visual memory, EF, dominant motor and sensory functioning, and non-dominant motor and sensory functioning.

As can be seen in Tables B.5, B.9, B.10, and B.11, linear relationships were observed across relevant study variables. Specifically, cognitive domains correlated with each other between .17 and .60. The covariates (estimated premorbid functioning; subject age; location of evaluation; use of antidepressants, anxiolytics, antipsychotics, analgesics, AEDs, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain) were also linearly related to cognitive domain performance, meeting the assumption of linearity of regression. As noted above, the data also conformed to the assumption of homogeneity of regression both at the multivariate and univariate levels.

Anticholinergic Medications

With regard to anticholinergic medications, a 3 (anticholinergic medication use) X 3 (polypharmacy) between subjects MANCOVA evaluated the interactions and main effects of medication use and polypharmacy across cognitive domains. Bartlett's test of sphericity was statistically significant (approximate chi square = 1145.41, $df = 44$, $p < .001$), indicating that the correlation of the dependent variables was sufficient to support the MANCOVA. Box's test of the equality of the variance-covariance matrices was also statistically significant [Box's M = 258.32, $F(180, 16076.90) = 1.26$, $p = .01$], suggesting

that the matrices were not homogenous. Therefore, Pillai's Trace was used to evaluate the multivariate effects because it is more robust to violations of this assumption compared to the other multivariate tests of significance.

The multivariate interaction of anticholinergic medication use X polypharmacy, when controlling for effects of the covariates, was examined prior to the multivariate main effects. The multivariate interaction effect on cognitive domain scores was not statistically significant [Pillai's Trace = .03, $F(9, 327) = 1.23$, $p = .27$, 1 – Wilks' lambda = .03]. The multivariate main effect of the following covariates were significant: location of the evaluation [Pillai's Trace = .19, $F(9, 327) = 8.37$, $p < .001$, 1-Wilks' lambda = .19], estimated premorbid functioning [Pillai's Trace = .50, $F(9, 327) = 35.57$, $p < .001$, 1-Wilks' lambda = .50], moderate to severe TBI [Pillai's Trace = .08, $F(9, 327) = 3.13$, $p = .001$, 1-Wilks' lambda = .08], cardiovascular diagnoses [Pillai's Trace = .08, $F(9, 327) = 3.20$, $p = .001$, 1-Wilks' lambda = .08], and respiratory diagnoses [Pillai's Trace = .06, $F(9, 327) = 2.27$, $p = .02$, 1-Wilks' lambda = .06]. The multivariate main effects of the independent variables of anticholinergic medication use and polypharmacy, were not statistically significant [Pillai's Trace = .01, $F(9, 327) = 0.45$, $p = .91$, 1-Wilks' lambda = .01; Pillai's Trace = .02, $F(9, 327) = 0.76$, $p = .65$, 1-Wilks' lambda = .02, respectively]. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no significant multivariate interaction between anticholinergic medication use and polypharmacy on cognitive functioning across domains. There also were not multivariate main effects of anticholinergic medication use or polypharmacy on cognitive functioning across domains.

Antidepressant Medications

With regard to antidepressant medications, a 3 (antidepressant medication use) X 3 (polypharmacy) between subjects MANCOVA evaluated the interactions and main effects of medication use and polypharmacy across cognitive domains. Bartlett's test of sphericity was statistically significant (approximate chi square = 1134.32, $df = 44$, $p < .001$), indicating that the correlation of the dependent variables was sufficient to support the MANCOVA. Box's test of the equality of the variance-covariance matrices was also statistically significant [Box's M = 226.21, $F(135, 51260.58) = 1.57$, $p < .001$], suggesting that the matrices were not homogenous. Therefore, Pillai's Trace was used to evaluate the multivariate effects because it is more robust to violations of this assumption compared to the other multivariate tests of significance.

The multivariate interaction of antidepressant medication use X polypharmacy, when controlling for effects of the covariates, was examined prior to the multivariate main effects. The multivariate interaction effect on cognitive domain scores was not statistically significant [Pillai's Trace = .04, $F(9, 325) = 1.51$, $p = .14$, 1 – Wilks' lambda = .04]. The multivariate main effect of the following covariates were significant: location of the evaluation [Pillai's Trace = .18, $F(9, 325) = 7.83$, $p < .001$, 1-Wilks' lambda = .18], estimated premorbid functioning [Pillai's Trace = .48, $F(9, 325) = 33.80$, $p < .001$, 1-Wilks' lambda = .48], moderate to severe TBI [Pillai's Trace = .08, $F(9, 325) = 3.17$, $p = .001$, 1-Wilks' lambda = .08], cardiovascular diagnoses [Pillai's Trace = .08, $F(9, 325) = 3.20$, $p = .001$, 1-Wilks' lambda = .08], and respiratory diagnoses [Pillai's Trace = .06, $F(9, 325) = 2.26$, $p = .02$, 1-Wilks' lambda = .06]. The multivariate main effects of the independent variables of antidepressant medication use and polypharmacy, were not

statistically significant [Pillai's Trace = .02, $F(9, 325) = 0.85$, $p = .57$, 1-Wilks' lambda = .02; Pillai's Trace = .02, $F(9, 325) = 0.73$, $p = .68$, 1-Wilks' lambda = .02, respectively]. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no significant multivariate interaction between antidepressant medication use and polypharmacy on cognitive functioning across domains. There also were not multivariate main effects of antidepressant medication use or polypharmacy on cognitive functioning across domains.

Anxiolytic Medications

With regard to anxiolytic medications, a 3 (anxiolytic medication use) X 3 (polypharmacy) between subjects MANCOVA evaluated the interaction and main effects of medication use and polypharmacy across cognitive domains. Bartlett's test of sphericity was statistically significant (approximate chi square = 1130.66, $df = 44$, $p < .001$), indicating that the correlation of the dependent variables was sufficient to support the MANCOVA. Box's test of the equality of the variance-covariance matrices was also statistically significant [Box's M = 280.78, $F(180, 17583.63) = 1.35$, $p = .001$], suggesting that the matrices were not homogenous. Therefore, Pillai's Trace was used to evaluate the multivariate effects because it is more robust to violations of this assumption compared to the other multivariate tests of significance.

The multivariate interaction of anxiolytic medication use X polypharmacy, when controlling for effects of the covariates, was examined prior to the multivariate main effects. The multivariate interaction effect on cognitive domain scores was not statistically significant [Pillai's Trace = .05, $F(9, 325) = 1.70$, $p = .09$, 1 – Wilks' lambda

= .05]. The multivariate main effect of the following covariates were significant: location of the evaluation [Pillai's Trace = .19, $F(9, 325) = 8.37$, $p < .001$, 1-Wilks' lambda = .19], estimated premorbid functioning [Pillai's Trace = .48, $F(9, 325) = 33.61$, $p < .001$, 1-Wilks' lambda = .48], moderate to severe TBI [Pillai's Trace = .08, $F(9, 325) = 3.17$, $p = .001$, 1-Wilks' lambda = .08], cardiovascular diagnoses [Pillai's Trace = .08, $F(9, 325) = 3.30$, $p < .001$, 1-Wilks' lambda = .08], and respiratory diagnoses [Pillai's Trace = .06, $F(9, 325) = 2.27$, $p = .02$, 1-Wilks' lambda = .06]. The multivariate main effects of the independent variables of anxiolytic medication use and polypharmacy, were not statistically significant [Pillai's Trace = .02, $F(9, 325) = 0.75$, $p = .66$, 1-Wilks' lambda = .02; Pillai's Trace = .03, $F(9, 325) = 0.98$, $p = .46$, 1-Wilks' lambda = .03, respectively]. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no significant multivariate interaction between anxiolytic medication use and polypharmacy on cognitive functioning across domains. There also were not multivariate main effects of anxiolytic medication use or polypharmacy on cognitive functioning across domains.

Analgesic Medications

With regard to anxiolytic medications, a 3 (analgesic medication use) X 3 (polypharmacy) between subjects MANCOVA evaluated the interaction and main effects of medication use and polypharmacy across cognitive domains. Bartlett's test of sphericity was statistically significant (approximate chi square = 1126.75, $df = 44$, $p < .001$), indicating that the correlation of the dependent variables was sufficient to support the MANCOVA. Box's test of the equality of the variance-covariance matrices was also

statistically significant [Box's M = 270.52, $F(180, 17470.74) = 1.30$, $p = .004$], suggesting that the matrices were not homogenous. Therefore, Pillai's Trace was used to evaluate the multivariate effects because it is more robust to violations of this assumption compared to the other multivariate tests of significance.

The multivariate interaction of analgesic medication use X polypharmacy, when controlling for effects of the covariates, was examined prior to the multivariate main effects. The multivariate interaction effect on cognitive domain scores was not statistically significant [Pillai's Trace = .04, $F(9, 325) = 1.37$, $p = .20$, 1 – Wilks' lambda = .04]. The multivariate main effect of the following covariates were significant: location of the evaluation [Pillai's Trace = .19, $F(9, 325) = 8.25$, $p < .001$, 1-Wilks' lambda = .19], estimated premorbid functioning [Pillai's Trace = .49, $F(9, 325) = 34.24$, $p < .001$, 1-Wilks' lambda = .49], moderate to severe TBI [Pillai's Trace = .08, $F(9, 325) = 3.27$, $p < .001$, 1-Wilks' lambda = .08], cardiovascular diagnoses [Pillai's Trace = .08, $F(9, 325) = 3.21$, $p < .001$, 1-Wilks' lambda = .08], and respiratory diagnoses [Pillai's Trace = .06, $F(9, 325) = 2.27$, $p = .02$, 1-Wilks' lambda = .06]. The multivariate main effects of the independent variables of analgesic medication use and polypharmacy, were not statistically significant [Pillai's Trace = .04, $F(9, 325) = 1.66$, $p = .10$, 1-Wilks' lambda = .04; Pillai's Trace = .02, $F(9, 325) = 0.81$, $p = .61$, 1-Wilks' lambda = .02, respectively]. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no significant multivariate interaction between analgesic medication use and polypharmacy on cognitive functioning across domains. There also were not multivariate main effects of analgesic medication use or

polypharmacy on cognitive functioning across domains.

Antiepileptic Medications

With regard to antiepileptic medications, a 3 (antiepileptic medication use) X 3 (polypharmacy) between subjects MANCOVA evaluated the interaction and main effects of medication use and polypharmacy across cognitive domains. Bartlett's test of sphericity was statistically significant (approximate chi square = 1127.40, $df = 44$, $p < .001$), indicating that the correlation of the dependent variables was sufficient to support the MANCOVA. Box's test of the equality of the variance-covariance matrices was also statistically significant [Box's M = 283.06, $F(180, 11870.59) = 1.36$, $p = .001$], suggesting that the matrices were not homogenous. Therefore, Pillai's Trace was used to evaluate the multivariate effects because it is more robust to violations of this assumption compared to the other multivariate tests of significance.

The multivariate interaction of antiepileptic medication use X polypharmacy, when controlling for effects of the covariates, was examined prior to the multivariate main effects. The multivariate interaction effect on cognitive domain scores was not statistically significant [Pillai's Trace = .02, $F(9, 325) = 0.76$, $p = .65$, 1 – Wilks' lambda = .02]. The multivariate main effect of the following covariates were significant: location of the evaluation [Pillai's Trace = .18, $F(9, 325) = 8.16$, $p < .001$, 1-Wilks' lambda = .18], estimated premorbid functioning [Pillai's Trace = .48, $F(9, 325) = 33.60$, $p < .001$, 1-Wilks' lambda = .48], moderate to severe TBI [Pillai's Trace = .08, $F(9, 325) = 3.19$, $p = .001$, 1-Wilks' lambda = .08], cardiovascular diagnoses [Pillai's Trace = .08, $F(9, 325) = 3.19$, $p = .001$, 1-Wilks' lambda = .08], and respiratory diagnoses [Pillai's Trace = .06, $F(9, 325) = 2.31$, $p = .02$, 1-Wilks' lambda = .06]. The multivariate main effects of the

independent variables of antiepileptic medication use and polypharmacy, were not statistically significant [Pillai's Trace = .04, $F(9, 325) = 1.61$, $p = .11$, 1-Wilks' lambda = .04; Pillai's Trace = .02, $F(9, 325) = 0.69$, $p = .72$, 1-Wilks' lambda = .02, respectively]. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no significant multivariate interaction between antiepileptic medication use and polypharmacy on cognitive functioning across domains. There also were not multivariate main effects of antiepileptic medication use or polypharmacy on cognitive functioning across domains.

Cardiovascular Medications

With regard to cardiovascular medications, a 3 (cardiovascular medication use) X 3 (polypharmacy) between subjects MANCOVA evaluated the interaction and main effects of medication use and polypharmacy across cognitive domains. Bartlett's test of sphericity was statistically significant (approximate chi square = 1126.04, $df = 44$, $p < .001$), indicating that the correlation of the dependent variables was sufficient to support the MANCOVA. Box's test of the equality of the variance-covariance matrices was also statistically significant [Box's M = 262.89, $F(180, 17816.35) = 1.28$, $p = .008$], suggesting that the matrices were not homogenous. Therefore, Pillai's Trace was used to evaluate the multivariate effects because it is more robust to violations of this assumption compared to the other multivariate tests of significance.

The multivariate interaction of cardiovascular medication use X polypharmacy, when controlling for effects of the covariates, was examined prior to the multivariate main effects. The multivariate interaction effect on cognitive domain scores was not

statistically significant [Pillai's Trace = .04, $F(9, 325) = 1.47$, $p = .16$, 1 – Wilks' lambda = .04]. The multivariate main effect of the following covariates were significant: location of the evaluation [Pillai's Trace = .19, $F(9, 325) = 8.33$, $p < .001$, 1-Wilks' lambda = .19], estimated premorbid functioning [Pillai's Trace = .49, $F(9, 325) = 33.98$, $p < .001$, 1-Wilks' lambda = .49], moderate to severe TBI [Pillai's Trace = .08, $F(9, 325) = 3.25$, $p < .001$, 1-Wilks' lambda = .08], cardiovascular diagnoses [Pillai's Trace = .08, $F(9, 325) = 3.18$, $p = .001$, 1-Wilks' lambda = .08], and respiratory diagnoses [Pillai's Trace = .06, $F(9, 325) = 2.27$, $p = .02$, 1-Wilks' lambda = .06]. The multivariate main effects of the independent variables of cardiovascular medication use and polypharmacy, were not statistically significant [Pillai's Trace = .04, $F(9, 325) = 1.37$, $p = .20$, 1-Wilks' lambda = .04; Pillai's Trace = .02, $F(9, 325) = 0.86$, $p = .57$, 1-Wilks' lambda = .02, respectively]. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no significant multivariate interaction between cardiovascular medication use and polypharmacy on cognitive functioning across domains. There also were not multivariate main effects of cardiovascular medication use or polypharmacy on cognitive functioning across domains.

Anti-Inflammatory Medications

With regard to anti-inflammatory medications, a 3 (anti-inflammatory medication use) X 3 (polypharmacy) between subjects MANCOVA evaluated the interaction and main effects of medication use and polypharmacy across cognitive domains. Bartlett's test of sphericity was statistically significant (approximate chi square = 1131.57, $df = 44$, $p < .001$), indicating that the correlation of the dependent variables was sufficient to

support the MANCOVA. Box's test of the equality of the variance-covariance matrices was also statistically significant [Box's M = 295.76, $F(180, 15030.91) = 1.36$, $p = .001$], suggesting that the matrices were not homogenous. Therefore, Pillai's Trace was used to evaluate the multivariate effects because it is more robust to violations of this assumption compared to the other multivariate tests of significance.

The multivariate interaction of anti-inflammatory medication use X polypharmacy, when controlling for effects of the covariates, was examined prior to the multivariate main effects. The multivariate interaction effect on cognitive domain scores was not statistically significant [Pillai's Trace = .01, $F(9, 325) = 0.44$, $p = .91$, 1 – Wilks' lambda = .01]. The multivariate main effect of the following covariates were significant: location of the evaluation [Pillai's Trace = .18, $F(9, 325) = 8.11$, $p < .001$, 1-Wilks' lambda = .18], estimated premorbid functioning [Pillai's Trace = .48, $F(9, 325) = 33.78$, $p < .001$, 1-Wilks' lambda = .48], moderate to severe TBI [Pillai's Trace = .08, $F(9, 325) = 3.17$, $p = .001$, 1-Wilks' lambda = .08], cardiovascular diagnoses [Pillai's Trace = .08, $F(9, 325) = 3.15$, $p = .001$, 1-Wilks' lambda = .08], and respiratory diagnoses [Pillai's Trace = .06, $F(9, 325) = 2.32$, $p = .02$, 1-Wilks' lambda = .06]. The multivariate main effects of the independent variables of anti-inflammatory medication use and polypharmacy, were not statistically significant [Pillai's Trace = .01, $F(9, 325) = 0.43$, $p = .92$, 1-Wilks' lambda = .01; Pillai's Trace = .03, $F(9, 325) = 0.94$, $p = .49$, 1-Wilks' lambda = .03, respectively]. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no significant multivariate interaction between anti-inflammatory medication use and polypharmacy on cognitive functioning

across domains. There also were not multivariate main effects of anti-inflammatory medication use or polypharmacy on cognitive functioning across domains.

Hormone Medications

With regard to hormone medications, a 3 (hormone medication use) X 3 (polypharmacy) between subjects MANCOVA evaluated the interaction and main effects of medication use and polypharmacy across cognitive domains. Bartlett's test of sphericity was statistically significant (approximate chi square = 1131.05, $df = 44$, $p < .001$), indicating that the correlation of the dependent variables was sufficient to support the MANCOVA. Box's test of the equality of the variance-covariance matrices was also statistically significant [Box's M = 287.01, $F(180, 13592.02) = 1.38$, $p < .001$], suggesting that the matrices were not homogenous. Therefore, Pillai's Trace was used to evaluate the multivariate effects because it is more robust to violations of this assumption compared to the other multivariate tests of significance.

The multivariate interaction of hormone medication use X polypharmacy, when controlling for effects of the covariates, was examined prior to the multivariate main effects. The multivariate interaction effect on cognitive domain scores was not statistically significant [Pillai's Trace = .03, $F(9, 325) = 1.18$, $p = .31$, 1 – Wilks' lambda = .03]. The multivariate main effect of the following covariates were significant: location of the evaluation [Pillai's Trace = .18, $F(9, 325) = 8.06$, $p < .001$, 1-Wilks' lambda = .18], estimated premorbid functioning [Pillai's Trace = .49, $F(9, 325) = 34.01$, $p < .001$, 1-Wilks' lambda = .49], moderate to severe TBI [Pillai's Trace = .08, $F(9, 325) = 3.26$, $p < .001$, 1-Wilks' lambda = .08], cardiovascular diagnoses [Pillai's Trace = .08, $F(9, 325) = 3.16$, $p = .001$, 1-Wilks' lambda = .08], and respiratory diagnoses [Pillai's Trace = .06,

$F(9, 325) = 2.28$, $p = .02$, 1-Wilks' lambda = .06]. The multivariate main effects of the independent variables of hormone medication use and polypharmacy, were not statistically significant [Pillai's Trace = .02, $F(9, 325) = 0.78$, $p = .64$, 1-Wilks' lambda = .02; Pillai's Trace = .03, $F(9, 325) = 0.97$, $p = .47$, 1-Wilks' lambda = .03, respectively]. Overall, despite adjusting for relevant variables, such as the neuropsychologist conducting the evaluation, estimated premorbid functioning, age, use of other medications, and diagnoses, there was no significant multivariate interaction between use of hormone medications and polypharmacy on cognitive functioning across domains. There also were not multivariate main effects of use of hormone medications or polypharmacy on cognitive functioning across domains.

CHAPTER VI

DISCUSSION

This study sought to add to and extend the literature regarding effects of medications and polypharmacy on cognition in a broad clinical sample (e.g., TBI, vascular/cerebrovascular accident [CVA], encephalitis, mental health diagnoses, etc.) using a comprehensive battery of neuropsychological tests. Collaborative and independent effects of medications and polypharmacy on cognitive functioning were thoroughly evaluated through three broad aims: 1) examining the effects of medication use and polypharmacy on global cognitive functioning, as assessed by OTBM; 2) examining the effects of medication use and polypharmacy on global cognitive functioning, as assessed by IIV; and 3) examining the effects of medication use and polypharmacy on domain-specific cognitive functioning. Additionally, the use of covariates in the analyses allowed for the relationships between cognitive performance and other variables in the sample (e.g., premorbid functioning, effects of underlying pathology related to diagnosis, effects of other prescribed medications) to be statistically controlled for, leaving a "purer" evaluation of the medication effects, addressing some of the limitations of previous studies (e.g., del Ser et al., 2019; Obermann et al., 2013).

To control for increased Type 1 error, and at times heterogeneity of variance, alpha values were variously corrected to .006 (Bonferroni corrected alpha) or .001 as appropriate. Regarding Aim One, results of the two-way ANCOVAs evaluating the

interaction and main effects of medication use and polypharmacy on the OTBM did not reveal a significant interaction or main effect of medication use or polypharmacy, as hypothesized. With regard to Aim Two, results of the two-way ANCOVAs evaluating the interaction and main effects of medication use and polypharmacy on IIV found no significant interactions between medication use and polypharmacy. However, three significant main effects were identified. There was a significant main effect for use of analgesics on IIV and a significant main effect of triptan on IIV, such that those who used these medications demonstrated higher cognitive variability (IIV) with regard to their performance across neuropsychological tests. There was also a significant main effect of polypharmacy on IIV, such that subjects without polypharmacy showed more cognitive variability than those taking more than 5 medications and those who were not taking any medications. Aim Three, which evaluated the interaction and main effects of medications and polypharmacy on domain-specific cognitive functioning using multivariate analyses, did not produce any significant interactions or main effects for medication use or polypharmacy.

Overall, the significant effects are interesting in that they suggest that the use of broad analgesics, and the use of triptans specifically, increase cognitive variability across a neuropsychological assessment, while polypharmacy reduces cognitive variability. While these findings may seem at odds with one another, they highlight a unique quality of cognitive variation: it can both positively and negatively impact cognition. Specifically, while many studies have identified associations between increased IIV and cognitive dysfunction (e.g., Ballard et al., 2001; Hill et al., 2013; Morgan et al., 2011; Murtha et al., 2002), some degree of cognitive variability is normal. For example, in their

evaluation of a sample of community dwelling adults, Schretlen et al. (2003) found that all subjects had a discrepancy of at least 1.6 SD between their highest and lowest scores on a comprehensive neuropsychological assessment. Additionally, two-thirds of these subjects had a discrepancy of more than three standard deviations between their highest and lowest scores.

Similarly, across various normative samples of healthy individuals, Binder et al. (2009) found that the median number of abnormal scores, defined as a score more than 1 SD away from the mean, was between 10 and 15% of the number of scores derived from the test battery. Therefore, on a neuropsychological assessment with at least 20 tests, such as that administered to participants in the current study, an individual will likely have at least two abnormal scores. However, the probability of obtaining low scores has also been associated with demographic characteristics, such as age and diverse ethnic and cultural backgrounds, and inversely related to intelligence and education (Iverson et al., 2008; Schretlen et al., 2003). Thus, those with higher intelligence are more likely to have some low scores and likely would have higher IIVs. On the other hand, those with greater probabilities of low scores due to various demographic characteristics will likely have an IIV that is constricted and lower than the IIV of the general population.

This is also true when considering the relationship between low scores and neurocognitive dysfunction. For those with severe, global cognitive impairment (e.g., later stages of dementia), there will likely be less variability with regard to neuropsychological test performance. This suggests that there is a curvilinear relationship between IIV and cognitive dysfunction. Although, additional research is needed to fully define this relationship.

Regardless, with the exception of a significant effect of broad analgesics, triptans, and polypharmacy on IIV, these findings suggest that use of anticholinergics, antidepressants, anxiolytics, analgesics, antiepileptics, cardiovascular, anti-inflammatory, and hormone medications, and the combination of both medication use and polypharmacy, do not significantly impact cognition on global or domain specific levels above and beyond effects of estimated premorbid functioning, age, other medication effects, and disease pathology. These findings are somewhat consistent with the current literature regarding effects of medication use on cognition.

Specifically, while fairly consistent cognitive deficits have been identified following use of some medications (e.g., anticholinergics and analgesics), similar to the relationship between analgesics and IIV illuminated here, many other therapeutic use groups (e.g., antidepressants, anxiolytics, and cardiovascular) have inconsistent findings regarding the relationship between medication use and cognition (see del Ser et al., 2019; Marpillat et al., 2013; Nevado-Holgado et al., 2016; Picton et al., 2018; Prado et al., 2018). Based on the literature, one factor that may lead to this variability in identifying cognitive effects across current literature, as well as the null results in the present study, is the demographics of the participants in the sample.

Sample Demographics

As noted above, the average age of sample subjects in the present study was approximately 40 years old (*SD* = 14.6). While some studies containing younger adults have identified cognitive deficits secondary to the use of medications (Nevado-Holgado et al., 2016), it appears that strong or consistent cognitive findings secondary to medication effects are most often identified in older adult populations (> 65; e.g.,

Campbell et al., 2009; Nader & Gowing, 2020; Obermann et al., 2013; Picton et al., 2018). This may be due to a number of reasons, including pharmacokinetic and pharmacodynamic factors or premorbid cognitive fragility causing older adults to be at higher risk of cognitive effects of medication use (Fulton & Allen, 2005; Kinirons & O'Mahony, 2004).

However, the clinical nature of the sample suggests that these participants may be more cognitively vulnerable than a sample of healthy adults. Nearly 20% of this sample was composed of individuals with a history of traumatic brain injury, nearly 10 % of this sample had a history of cardiovascular disorders, and approximately 6% of this sample were diagnosed with SMI. Individuals with these diagnoses are at heightened risk of cognitive dysfunction (Almeida et al., 2019; Huang et al., 2018; Kuller et al., 2005), like older adults. Additionally, over 6% of the sample were diagnosed with various neurocognitive disorders, suggesting that while the overall sample was composed of younger adults, a majority of the sample consisted of those who may not have had significant cognitive reserve to compensate for medication effects, if they were present. Despite this, no significant effects of medications were identified for OTBM or domain means and the only significant medication effects identified, above and beyond that of disease processes, were for the use of analgesic medications, the use of triptans, and polypharmacy, on cognitive variability.

Polypharmacy.

Older adults also have higher rates of medication use and polypharmacy (Barnett et al., 2012; Kantor et al., 2015), which has been suggested as adding to the risk of cognitive dysfunction in older adults (Jyrkkä et al., 2011; Maher et al., 2014; Moore &

O'Keefe, 1999; Sordahl et al., 2019). While an effect of polypharmacy on IIV was identified, this relationship was only significant in one analysis and no significant effects of polypharmacy were found on overall cognition as measured by the OTBM or at the domain level, as has been suggested in the previous literature. These mostly null findings may have been due to the relatively low rate of polypharmacy in the current sample (11%). However, it is also possible that the previous findings of significant effects of polypharmacy on cognition were due to more than simply the number of medications used.

For example, studies by Lam (2017) and Risacher et al. (2016) indicate that the effects of polypharmacy on cognition are particularly salient when resulting from the use of multiple anticholinergic drugs. Specifically, the use of one anticholinergic drug in the context of other medications may not lead to cognitive impairment. Rather, it is the overall anticholinergic burden which leads to cognitive impairment. While evaluating for the overall burden of specific medications was beyond the scope of this study, it is possible that low burden could have contributed to some of the null findings.

Medication.

In addition to the potential of medication burden effects, which were not able to be evaluated in the present study, there are several other variables that may have contributed to the present findings, despite generally findings of cognitive effects of anticholinergics, benzodiazepine anxiolytics, opioid analgesics, and AEDs in the previous literature. Specifically, medication dosage, duration of use, frequency of use, and when the medication was taken in relation to the date and time of the neuropsychological assessment would each affect a drug's response, and subsequently the effect of the drug

on cognition. Unfortunately, these variables were not available for study participants given the archival nature of the data. Further, information regarding the reason for the prescription medication use or what specific diagnosis it was prescribed to treat were also not available in the current sample. Therefore, while classifications of medications were based on chemical compositions, the true therapeutic use of many medications was unknown given that many medications can be used for various purposes depending on does and frequency of use. This further complicates the medication use classifications and analyses of the current sample. While some of these variables were considered in previous literature, such as long-term use of benzodiazepines (Nader & Gowing, 2020), opioids (Allegri et al., 2019) and AEDs (Park & Kwon, 2008; Stein & Strickland,1998), further consideration should be given to evaluation of each of these variables in the context of effects on cognitive functioning in future studies.

Diagnoses and Estimated Premorbid Functioning.

Results of this study also underlined the importance of controlling for neurological, psychological, and general health diagnoses, as well as estimated premorbid functioning when evaluating the cognitive effects of medication. Specifically, significant effects of moderate to severe TBI and the presence of a cardiovascular diagnosis on overall cognition, as measured by OTBM and IIV, and domain-specific cognition were identified for all univariate and multivariate analyses. Significant effects of estimated premorbid functioning were also identified for all analyses of OTBM and domain means. Further, many analyses also showed significant effects of neurocognitive disorders and respiratory disorders on cognition.

Despite the clear influence of premorbid functioning and these various disease

processes on cognitive functioning, no known studies to date have controlled for both premorbid functioning and physical, psychiatric, and medical diagnoses when evaluating the relationship between medication use and cognitive functioning. Therefore, in the context of significant main effects of analgesics, triptans, and polypharmacy on IIV only, questions remain regarding the validity of many of the previously identified relationships between medication use and cognition. Additional studies of these effects while controlling for these factors are necessary to fully understand the extent of the contributions from premorbid functioning and underlying disease processes on previously identified medication effects.

Neuropsychological Test Battery

Another factor that may have led to the variability in cognitive effects across current literature compared to the largely null results in the present study, is the use of a comprehensive battery of neuropsychological tests to evaluate cognitive functioning. As previously discussed, most of the previous studies examining the cognitive effects of medication used screening tests, such as the MMSE (Folstein et al., 1975), to evaluate global cognitive status. While this type of measure has benefits in briefly assessing cognition within the research setting, there are significant limitations to using such tests. Specifically, while screening measures are ideally sensitive and specific to cognitive dysfunction, this is not always the case. For example, in a heart failure population one study found that at a cut value of < 24, the MMSE only correctly identified 28% of individuals as having cognitive impairment, while nearly 10% of cognitively normal individuals were incorrected identified as having cognitive impairment (Hawkins et al., 2014). Using a more conservative cut-off (<29/30), Hoops et al. (2009) found that the

MMSE correctly identified 92% of individuals with mild cognitive impairment in the context of Parkinson's disease. However, 58% of cognitively normal individuals were also identified as having mild cognitive impairment. Given that many of the previous studies evaluating the cognitive effects of medication showed small to medium effect sizes and were plagued by small sample sizes, the use of screening measures to identify cognitive impairment, such as the MMSE, may further explain the discrepancies.

Even when specific neuropsychological tests are utilized to examine cognitive impairment, such as Trail Making Test (e.g., Allegri et al., 2019; Baldacchino et al., 2012), there is significantly more risk of erroneously concluding impairment or a lack of impairment when researchers do not use a comprehensive battery of neuropsychological tests. This is because, as previously discussed, some degree of cognitive variability is normal (Binder et al., 2009; Schretlen et al., 2003). When combining scores across multiple tests from the same domain within a comprehensive test battery, such as with the MNS used in this study, the risk of Type I error is reduced. Additionally, given the number of analyses conducted, and at times heterogeneity of variance, corrected significance values were used in the present study to further reduce risk of false positive findings.

Trends

Using these criteria, the only significant effects were found for use of broad analgesic medications, triptans, and polypharmacy on IIV at .001 and .006 alpha levels. However, there were other effects that were trending towards significance at this higher level. Specifically, significant interactions between use of anxiolytics and polypharmacy on OTBM (p=.01) and on IIV (p=.03) were identified, as were significant interactions

between AEDs and polypharmacy on OTBM (p=.03) and on IIV (p=.03). A main effect of analgesics on OTBM, as well as main effects of polypharmacy on IIV when run with anticholinergic drugs, antidepressants, analgesics, cardiovascular medications, anti-inflammatory medications, and hormone medications were also identified at $p < .05$.

Overall, the pattern of these results continues to fit with the previous literature and suggest that most medications do not have significant effects on cognitive functioning when accounting for estimated premorbid functioning, the neuropsychologist who supervised the evaluation, use of other medications and various diagnoses. Small differential effects of anxiolytics and AEDs on the OTBM and IIV were identified. Although, these differences appear to be only in the context of polypharmacy. Consistent with the previously discussed results, a main effect of analgesic use on global cognitive functioning appears to be present when assessed by OTBM, as well as when assessed by IIV. This pattern also provides added support for the effects of polypharmacy on IIV across other medication use groups.

Interestingly, when evaluating global cognitive effects, significant effects on the OTBM were rarely identified. Rather, more often, significant interaction and main effects for both medication use and polypharmacy were either significant for differences in both OTBM and IIV, or IIV independently. Additionally, no significant multivariate analyses assessing medication use and polypharmacy across cognitive domains were significant at conservative or typical alpha values. This pattern suggests that IIV may be particularly sensitive to the effects of medication use and polypharmacy on cognition and provide additional support for the use of this valuable metric of cognitive functioning in the context of neuropsychological assessment in a clinical sample of younger adults.

Implications

While this study was exploratory in nature, the findings have clinical relevance for physicians, neurologists, and neuropsychologists given that these physicians are often asked to identify and differentiate cognitive "signal" from "noise" through cognitive assessment following complaints of subjective cognitive change (Schoenberg & Scott, 2011). The current results provide evidence for small effects of analgesics, triptans, and polypharmacy on cognitive IIV in this younger adult, clinical sample. These findings are above and beyond the effects of premorbid functioning; neurological, psychiatric, and general medical diagnoses; and use of other medications. However, while these effects were statistically significant, differences in IIV only equated to negligible differences in terms of clinical relevance across all significant results. For example, differences in IIV for analgesics triptans, and polypharmacy were within 1-3 points of the other groups.

Given that recommendations to interpret significant discrepancies on neuropsychological tests ranges from 1 to 2 SD (Lezak et al., 2012), the differences identified in this study do not constitute clinically significant discrepancies in cognitive functioning from a neuropsychological perspective. In conjunction with the otherwise null results, this study provides support for younger adults' relative resistance to significant cognitive effects of the medications evaluated in the present study. Therefore, it would be highly unlikely for most of the medications evaluated in this study to produce any more than a mild changes to variability on neurocognitive performance for younger adults, even those from a clinical, cognitively vulnerable sample.

Limitations

Despite this, it is important to recognize some important limitations to the present study. First, while the overall sample size was large and it surpassed the minimal sample size identified by the a priori power analysis, due to the wide variety of medications reported by study subjects, not all medication groups had sufficient data to support an analysis. Due to this issue, a deductive approach to data analysis was employed. However, it is possible that because analyses were first run with the therapeutic use group category, specific effects of a drug class or specific medication were outweighed by the effects, or lack thereof, of the other drug classes.

Additionally, given the high number of different medications reported, further caution had to be used when running analyses with sufficiently populated groups. Specifically, given that familywise error rate increases with the number of analyses, a Bonferroni corrected alpha was used to reduce the chance of Type I error. The alpha was further reduced in the event of violations of homogeneity of variance, which was not uncommon, particularly given the distribution of medications across the sample. While this helped reduce the risk of false positive errors, it is possible that legitimate interactions and main effects of medications and polypharmacy on global and domain specific cognitive functioning were not interpreted.

Finally, given the circumstances regarding neuropsychological evaluations and the archival nature of the data, some data that would have aided in more accurate classifications and evaluations of medication use was missing. Specifically, all information regarding medication use and diagnoses was provided by the patient, and not a comprehensive medical record system. Thus, it is possible that some of the reported

medication and diagnosis information is inaccurate or incomplete. Additionally, information regarding why a medication had been prescribed, the dosage of medications, frequency of medication use, when the subject last took a dose of medication in relation to the date and time of the neuropsychological assessment, and how long the patient had been taking their medications was not available. These missing factors limit our understanding of the study results.

Future Directions

Further evaluation of the cognitive effects of medication use with a larger sample size and more comprehensive medication information (e.g., dose, frequency of administration, duration of use, reason for use, etc.) is warranted. While the present study provides a comprehensive baseline of the effects of medications and polypharmacy on cognition in a relatively young clinical sample, future studies should explore the effects of medication in older clinical and non-clinical samples using this comprehensive methodology to provide a more complete picture of the potential effects of these medications on comprehensive neuropsychological tests. Additionally, while this study focused exclusively on the use of prescription medications and their effects on cognition, future studies should also explore the use and effects of over-the-counter medications and dietary supplements on cognition. Much like the use of prescription medications, the use of dietary supplements has increased over time (Qato et al., 2016). Given that dietary supplements do not require FDA approval, the potential for unknown cognitive side effects in these substances is high.

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APPENDICES

Appendix A - IRB Approval Letter

irb@southalabama.edu

UNIVERSITY OF SOUTH ALABAMA

TELEPHONE: (251) 460-6308
AD 240 · MOBILE, AL. 36688-0002

INSTITUTIONAL REVIEW BOARD
October 29, 2019

Principal Investigator:	Sarah Taylor		
IRB # and Title:	IRB PROTOCOL: 19-421 [1514616-1] THE EFFECT OF MEDICATION ON COGNITION: INFORMATION FROM A CLINICAL SAMPLE USING A SEMI-FLEXIBLE BATTERY OF COMMON NEUROPSYCHOLOGICAL TESTS		
Status:	APPROVED	Review Type:	Exempt Review
Approval Date:	October 29, 2019	Submission Type:	New Project
Initial Approval:	October 29, 2019	Expiration Date:	
Review Category:	45 CFR 46.104(d)(4): Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens: ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects		

This panel, operating under the authority of the DHHS Office for Human Research and Protection, assurance number FWA 00001602, and IRB Database #00000286, has reviewed the submitted materials for the following:

1. *Protection of the rights and the welfare of human subjects involved.*
2. *The methods used to secure and the appropriateness of informed consent.*
3. *The risk and potential benefits to the subject.*

The regulations require that the investigator not initiate any changes in the research without prior IRB approval, except where necessary to eliminate immediate hazards to the human subjects, and that **all problems involving risks and adverse events be reported to the IRB immediately!**

Subsequent supporting documents that have been approved will be stamped with an IRB approval and expiration date (if applicable) on every page. Copies of the supporting documents must be utilized with the current IRB approval stamp unless consent has been waived.

Notes:

Appendix B – Demographic and Correlation Tables

Table B.1
Frequency of Diagnoses for Study Participants

Diagnosis	*n* (Valid %)
Internalizing Disorders	230 (46.3%)
Depression	173 (43.3%)
Anxiety	106 (26.5%)
PTSD	8 (2.0%)
Panic Disorder	7 (1.8%)
OCD	3 (0.8%)
Somatic Symptom Disorder	23 (5.8%)
Conversion Disorder	14 (3.5%)
Impulse Control Disorder	1 (0.3%)
Substance Use Disorder	66 (13.3%)
Severe Mental Illness	23 (5.8%)
Schizophrenia	5 (1.3%)
Bipolar Disorder	16 (4.0%)
Other Psychotic Disorders	2 (0.5%)
Learning Disorders	85 (21.3%)
Learning Disability	59 (14.8%)
ADHD	39 (9.8%)
Neurodevelopmental Disorders	20 (5.0%)
ASD	6 (1.5%)
Developmental Motor Disorders	3 (0.8%)
Borderline Intellectual Functioning	9 (2.3%)
Intellectual Disability	2 (0.5%)
Seizure Disorder	18 (4.5%)
Neurocognitive Disorders	25 (6.3%)
Alzheimer's Disease	6 (1.5%)
Cerebrovascular Disease	8 (2.0%)
FTLD	1 (0.3%)
Parkinson's Disease	1 (0.3%)
Dementia	16 (4.0%)
Multiple Sclerosis	9 (2.3%)
Viral Encephalitis	3 (0.8%)

Table B.1 Cont.

Diagnosis	*n* (Valid %)
Chiari Malformation	3 (0.8%)
Brain Tumor	7 (1.8%)
Traumatic Brain Injury	71 (17.8%)
Post Concussive Syndrome	7 (1.8%)
Mild TBI	48 (12.0%)
Moderate to Severe TBI	21 (5.3%)
Cardiovascular Disorders	37 (9.3%)
Cardiac Disease	5 (1.3%)
Stroke	19 (4.8%)
Transient Ischemic Attack	3 (0.8%)
Aneurysm	4 (1.0%)
Hyperlipidemia	7 (1.8%)
Autoimmune Disorders	10 (2.5%)
Thyroid Dysfunction	5 (1.3%)
Lupus	2 (0.5%)
Diabetes	4 (1.0%)
Hyperchloremia	1 (0.3%)
Respiratory Dysfunction	17 (4.3%)
Sleep Apnea	12 (3.0%)
Asthma	4 (1.0%)
Chronic Obstructive Pulmonary Disease	1 (0.3%)
Gastrointestinal	6 (1.5%)
Inflammatory Bowel Diseases	5 (1.3%)
Gastroesophageal Reflux Disease	2 (0.5%)
Pain	74 (18.5%)
Migraine	19 (4.8%)
Tinnitus	1 (0.3%)
Eating Disorders	2 (0.4%)
Sleep Disorders	8 (2.0%)
Sleep Disturbance	7 (1.8%)
Narcolepsy	1 (0.3%)

Note. n = 497. PTSD = Post-traumatic Stress Disorder. OCD = Obsessive Compulsive Disorder. ADHD = Attention-Deficit/Hyperactivity Disorder. ASD = Autism Spectrum Disorder. FTLD = Frontotemporal Lobar Degeneration. TBI = Traumatic Brain Injury.

Table B.2

Frequency of Medication Use by Study Participants

Therapeutic Use	Drug Family	Drug Name (Generic)	n (Valid %)
Anticholinergics			**100 (20.1%)**
Antidepressants			**232 (46.7%)**
	Atypical Antidepressants		67(13.5%)
		Bupropion	37 (7.4%)
		Mirtazapine	8 (1.6%)
		Nefazodone	9 (1.8%)
		Trazodone	19 (3.8%)
	SNRI		33 (6.6%)
		Desvenlafaxine	2 (0.4%)
		Duloxetine	5 (1.0%)
		Levomilnacipran	1 (0.2%)
		Venlafaxine	25 (5.0%)
	SSRI		138 (27.8%)
		Citalopram	17 (3.4%)
		Escitalopram	15 (3.0%)
		Fluoxetine	26 (5.2%)
		Fluvoxamine	2 (0.4%)
		Paroxetine	30 (6.0%)
		Sertraline	46 (9.3%)
		Vortioxetine	2 (0.4%)
	Tricyclics		43 (8.7%)
		Amitriptyline	29 (5.8%)
		Doxepin	1 (0.2%)
		Imipramine	4 (0.8%)
		Nortriptyline	4 (0.8%)
		Cyclobenzaprine	5 (1.0%)
Anxiolytics			**68 (13.7%)**
	Benzodiazepines		51 (10.3%)
		Alprazolam	20 (4.0%)
		Chlordiazepoxide	1 (0.2%)
		Clonazepam	13 (2.6%)
		Diazepam	3 (0.6%)
		Eszopiclone	1 (0.2%)
		Lorazepam	12 (2.4%)
		Temazepam	1 (0.2%)

Table B.2 Cont.

Therapeutic Use	Drug Family	Drug Name (Generic)	n (Valid %)
		Triazolam	1 (0.2%)
	Benzodiazepine-Like		8 (1.6%)
		Zolpidem	8 (1.6%)
	Other Anxiolytics		13 (2.6%)
		Buspirone	13 (2.6%)
Antipsychotics			**37(7.4%)**
	Atypical Antipsychotics		35 (7.0%)
		Aripiprazole	3 (0.6%)
		Brexpiprazole	2 (0.4%)
		Olanzapine	10 (2.0%)
		Risperidone	7 (1.4%)
		Quetiapine	15 (3.0%)
	Phenothiazines		1 (0.2%)
		Prochlorperazine	1 (0.2%)
	Butyrophenones		1 (0.2%)
		Haloperidol	1 (0.2%)
Mood Stabilizers			**4 (0.8%)**
	Antimanic Agents		4 (0.8%)
		Lithium	4 (0.8%)
Analgesics			**67 (13.5%)**
	Triptans		6 (1.2%)
		Almotriptan	1 (0.2%)
		Eletriptan	1 (0.2%)
		Rizatriptan	2 (0.4%)
		Sumatriptan	2 (0.4%)
	Opioids		38 (7.6%)
		Buprenorphine	1 (0.2%)
		Dextropropoxyphene	9 (1.8%)
		Fentanyl	2 (0.4%)
		Hydrocodone	7 (1.4%)
		Oxycodone	2 (0.4%)
		Tramadol	19 (3.8%)
	Opioid Combinations		20 (4.0%)
		Hydrocodone-Acetaminophen	5 (1.0%)
		Hydrocodone Bitartrate-Acetaminophen	10 (2.0%)
		Hydrocodone-Chlorpheniramine	1 (0.2%)

Table B.2 Cont.

Therapeutic Use	Drug Family	Drug Name (Generic)	n (Valid %)
		Oxycodone-Acetaminophen	2 (0.4%)
		Propoxyphene-Acetaminophen	2 (0.4%)
	Non-Opioid		11 (2.2%)
		Acetaminophen	11 (2.2%)
Addiction			**5 (1.0%)**
	Alcohol Antagonist		1 (0.2%)
		Disulfiram	1 (0.2%)
	Opioid Agonist		4 (0.8%)
		Buprenorphine-Naloxone	1 (0.2%)
		Methadone	3 (0.6%)
Antiepileptics			**96 (19.3%)**
	Traditional AEDs		47 (9.5%)
		Carbamazepine	10 (2.0%)
		Phenytoin	13 (2.6%)
		Primidone	1 (0.2%)
		Divalproex Sodium	24 (4.8%)
	Newer AEDs		56 (11.3%)
		Oxcarbazepine	3 (0.6%)
		Gabapentin	33 (6.6%)
		Lamotrigine	15 (3.0%)
		Levetiracetam	5 (1.0%)
		Topiramate	2 (0.4%)
Stimulants			**21 (4.2%)**
	Amphetamine Combinations		13 (2.6%)
		Dextroamphetamine-Amphetamine	11 (2.2%)
	Centrally Acting Sympathomimetics		12 (2.4%)
		Lisdexamfetamine	2 (0.4%)
		Methylphenidate	6 (1.2%)
		Modafinil	3 (0.6%)
		Pemoline	1 (0.2%)
Antidementia			**6 (1.2%)**
	Cholinesterase Inhibitors		5 (1.0%)
		Donepezil	5 (1.0%)
	NMDA Antagonists		1 (0.2%)
		Memantine	1 (0.2%)
Cardiovascular			**86 (17.3%)**

Table B.2 Cont.

Therapeutic Use	Drug Family	Drug Name (Generic)	n (Valid %)
	ACE Inhibitors		29 (5.8%)
		Benazepril	3 (0.6%)
		Fosinopril	3 (0.6%)
		Lisinopril	9 (1.8%)
		Moexipril	1 (0.2%)
		Quinapril	11 (2.2%)
		Ramipril	2 (0.4%)
	Alpha-Adrenergic Blockers		5 (1.0%)
		Doxazosin	3 (0.6%)
		Prazosin	2 (0.4%)
	Angiotensin II Receptor Blockers		8 (1.6%)
		Candesartan	1 (0.2%)
		Losartan	5 (1.0%)
		Olmesartan	1 (0.2%)
		Valsartan	1 (0.2%)
	Beta Blockers		25 (5.0%)
		Atenolol	4 (0.8%)
		Betaxolol	1 (0.2%)
		Labetalol	3 (0.6%)
		Metoprolol	12 (2.4%)
		Nebivolol	1 (0.2%)
		Propranolol	4 (0.8%)
	Calcium Channel Blockers		18 (3.6%)
		Amlodipine	9 (1.8%)
		Diltiazem	6 (1.2%)
		Nifedipine	3 (0.6%)
		Verapamil	1 (0.2%)
	Cardiac Glycosides		4 (0.8%)
		Digoxin	4 (0.8%)
	Centrally Acting Alpha2 Agonist		5 (1.0%)
		Clonidine	5 (1.0%)
	Diuretics		23 (4.6%)
		Hydrochlorothiazide	17 (3.4%)
		Furosemide	4 (0.8%)
		Spironolactone	3 (0.6%)
	Nitrates		3 (0.6%)
		Isosorbide mononitrate	3 (0.6%)

Table B.2 Cont.

Therapeutic Use	Drug Family	Drug Name (Generic)	n (Valid %)
	Sodium Channel Blockers		1 (0.2%)
		Lidocaine	1 (0.2%)
Lipid Modifying Agents			**41 (8.2%)**
	Fibrates		4 (0.8%)
		Fenofibrate	3 (0.6%)
		Gemfibrozil	1 (0.2%)
	HMG-CoA Reductase Inhibitors		38 (7.6%)
		Atorvastatin	25 (5.0%)
		Pravastatin	3 (0.6%)
		Rosuvastatin	3 (0.6%)
		Simvastatin	7 (1.4%)
Antithrombotic Agents			**15 (3.0%)**
	Anticoagulants		10 (2.0%)
		Enoxaparin	1 (0.2%)
		Warfarin	9 (1.8%)
	Antiplatelet		6 (1.2%)
		Clopidogrel	6 (1.2%)
Anti-Inflammatory			**79 (15.9%)**
	Corticosteroids		5 (1.0%)
		Dexamethasone	1 (0.2%)
		Prednisone	4 (0.8%)
	Second-Generation NSAID		25 (5.0%)
		Celecoxib	13 (2.6%)
		Rofecoxib	12 (2.4%)
	First-Generation NSAID		57 (11.5%)
		Aspirin	27 (5.4%)
		Diclofenac	1 (0.2%)
		Diflunisal	1 (0.2%)
		Ibuprofen	21 (4.2%)
		Naproxen	1 (0.2%)
		Relafen	1 (0.2%)
		Ketorolac	1 (0.2%)
		Sulindac	1 (0.2%)
		Indomethacin	2 (0.4%)
		Meloxicam	2 (0.4%)
Hormones			**79 (15.9%)**
	Contraceptives		14 (2.8%)

Table B.2 Cont.

Therapeutic Use	Drug Family	Drug Name (Generic)	n (Valid %)
		Medroxyprogesterone Acetate	3 (0.6%)
		Progesterone	2 (0.4%)
	Non-contraceptives		69(13.9%)
		Estrogens	26 (5.2%)
		Levothyroxine	45 (9.1%)
		Raloxifene	3 (0.6%)
Respiratory			**27 (5.4%)**
	Bronchodilators		20 (4.0%)
		Albuterol	15 (3.0%)
		Alupent	1 (0.2%)
		Salmeterol	5 (1.0%)
		Theophylline	1 (0.2%)
		Tiotropium bromide	1 (0.2%)
	Corticosteroids		9 (1.8%)
		Flunisolide	2 (0.4%)
		Fluticasone	7 (1.4%)
	Nonopioid Antitussives		1 (0.2%)
		Benzonatate	1 (0.2%)
	Leukotriene Modifiers		6 (1.2%)
		Montelukast	6 (1.2%)
Antidiabetics			**25 (5.0%)**
	Biguanides		10 (2.0%)
		Metformin	10 (2.0%)
	Incretin Mimetics		1 (0.2%)
		Liraglutide	1 (0.2%)
	Insulin Preparations		10 (2.0%)
		Insulin	10 (2.0%)
	Meglitinides		1 (0.2%)
		Repaglinide	1 (0.2%)
	SGLT-2 Inhibitor		1 (0.2%)
		Dapagliflozin	1 (0.2%)
	Sulfonylureas		3 (0.6%)
		Glyburide (Glibenclamide)	1 (0.2%)
		Glipizide	2 (0.4%)
	Thiazolidinediones		3 (0.6%)
		Pioglitazone	3 (0.6%)
Antihistamines			**24 (4.8%)**
	First-Generation H1 Antagonist		9 (1.8%)

Table B.2 Cont.

Therapeutic Use	Drug Family	Drug Name (Generic)	n (Valid %)
		Chlorpheniramine-Methscopolamine-Phenylephrine	1 (0.2%)
		Diphenhydramine	1 (0.2%)
		Hydroxyzine	5 (1.0%)
		Meclizine	1 (0.2%)
		Promethazine	1 (0.2%)
	Second-Generation H1 Antagonist		15 (3.0%)
		Cetirizine	5 (1.0%)
		Desloratadine	1 (0.2%)
		Fexofenadine	5 (1.0%)
		Loratadine	3 (0.6%)
		Azelastine	1 (0.2%)
Urological			**15 (3.0%)**
	Alpha-adrenergic Antagonists		2 (0.4%)
		Terazosin	1 (0.2%)
		Tamsulosin	1 (0.2%)
	Anticholinergic		12 (2.4%)
		Oxybutynin	7 (1.4%)
		Solifenacin	3 (0.6%)
		Tolterodine	2 (0.4%)
	Phosphodiesterase Type 5 Inhibitor		1 (0.2%)
		Sildenafil	1 (0.2%)
	5-Alpha-Reductase Inhibitors		1 (0.2%)
		Finasteride	1 (0.2%)
Gastrointestinal			**65 (13.1%)**
	Antispasmodic		3 (0.6%)
		Dicycloverine	3 (0.6%)
	Gallstone Dilution Agents		1 (0.2%)
		Ursodiol	1 (0.2%)
	H2-Receptor Antagonists		8 (1.6%)
		Cimetidine	1 (0.2%)
		Ranitidine	7 (1.4%)
	Prokinetic		3 (0.6%)
		Metoclopramide	3 (0.6%)
	Proton Pump Inhibitors		47 (9.5%)

Table B.2 Cont.

Therapeutic Use	Drug Family	Drug Name (Generic)	n (Valid %)
		Esomeprazole	9 (1.8%)
		Lansoprazole	12 (2.4%)
		Omeprazole	21 (4.2%)
		Pantoprazole	5 (1.0%)
		Rabeprazole	1 (0.2%)
	Stool Softener		7 (1.4%)
		Docusate Sodium	7 (1.4%)
Muscle Relaxants			**14 (2.8%)**
	Centrally Acting		13 (2.6%)
		Baclofen	2 (0.4%)
		Metaxalone	6 (1.2%)
		Methocarbamol	2 (0.4%)
		Tizanidine	3 (0.6%)
	Peripherally Acting		1 (0.2%)
		Orphenadrine	1 (0.2%)
Calcium and Bone Mineralization			**5 (1.0%)**
	Bisphosphonates		5 (1.0%)
		Alendronic Acid	2 (0.4%)
		Risedronic Acid	3 (0.6%)
Immunomodulators			**6 (1.2%)**
	Immunostimulants		4 (0.8%)
		Glatiramer Acetate	2 (0.4%)
		Interferon Beta-1a	2 (0.4%)
	Immunosuppressants		2 (0.4%)
		Etanercept	1 (0.2%)
		Methotrexate	2 (0.4%)
Movement Disorder			**5 (1.0%)**
	Dopamine-Releasing Agent		1 (0.2%)
		Amantadine	1 (0.2%)
	Dopamine Replacement		2 (0.4%)
		Levodopa-Carbidopa	2 (0.4%)
	Dopamine Agonist		2 (0.4%)
		Ropinirole	2 (0.4%)
Antiglaucoma			**3 (0.6%)**
	CAI		2 (0.4%)
		Acetazolamide	2 (0.4%)
	Prostaglandin Analogs		1 (0.2%)
		Travoprost	1 (0.2%)

Table B.2 Cont.

Therapeutic Use	Drug Family	Drug Name (Generic)	n (Valid %)
	Other Antiglaucomas		1 (0.2%)
		Dipivefrine	1 (0.2%)
Dermatological			**3 (0.6%)**
	Anti-infectives		1 (0.2%)
		Fluconazole	1 (0.2%)
	Corticosteroids		2 (0.4%)
		Clobetasol	2 (0.4%)
Antimalarial			**2 (0.4%)**
	Aminoquinolines		2 (0.4%)
		Hydroxychloroquine	2 (0.4%)
Cytotoxic Drugs			**2 (0.4%)**
	Alkylating Agents		2 (0.4%)
		Temozolomide	2 (0.4%)
Weight Loss Drugs			**2 (0.4%)**
	Lipase Inhibitor		1 (0.2%)
		Orlistat	1 (0.2%)
	Sympathomimetic Amines		1 (0.2%)
		Phentermine	1 (0.2%)
Antigout Agents			**1 (0.2%)**
	Uric Acid Inhibitors		1 (0.2%)
		Allopurinol	1 (0.2%)

Note. N = 497. SNRI = Serotonin-Norepinephrine Reuptake Inhibitor. SSRI = Selective Serotonin Reuptake Inhibitor. AED = Antiepileptic Drug. NMDA = N-Methyl-D-aspartate receptor. ACE = Angiotensin-Converting Enzyme. HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A. NSAID = Non-Steroidal Anti-Inflammatory Drug. SGLT-2 = Sodium-Glucose Co-Transporter 2. CAI = Carbonic Anhydrase Inhibitor. Due to some participants having prescriptions for multiple medications within the same drug family and/or therapeutic use group, frequency of the larger groups are not always equivalent to the frequency of use identified at the drug-name level.

Table B.3

Medications with Strongly Anticholinergic used by Study Participants

Therapeutic Use	Drug Family	Drug Name (Generic)
Antidepressants		
	Atypical Antidepressants	
		Paroxetine
	Tricyclics	
		Amitriptyline
		Doxepin
		Imipramine
		Nortriptyline
		Cyclobenzaprine
Analgesics		
	Opioid Combinations	
		Hydrocodone-Chlorpheniramine
Antipsychotics		
	Atypical Antipsychotics	
		Olanzapine
	Phenothiazines	
		Prochlorperazine
Antihistamines		
	First-Generation H1 Antagonist	
		Methscopolamine-Phenylephrine
		Diphenhydramine
		Hydroxyzine
		Meclizine
		Promethazine
Urological		
	Anticholinergic	
		Oxybutynin
Gastrointestinal		
	Antispasmodic	
		Dicycloverine
Muscle Relaxants		
	Peripherally Acting	
		Orphenadrine

Table B.4

Meyers Neuropsychological Battery and Supplemental Tests by Domain

#	Test Name	Cognitive Function	Hypothesized Localization(s)	Reference
00	*Performance Validity*[a]			
	1) Word Memory Test (Green, 2003)	Validity and verbal memory recall and recognition	Relatively insensitive to cognitive impairment	Lezak et al., 2004 (p. 850-851); Strauss et al., 2006
	2) Test of Memory Malingering (Tombaugh, 1996)	Validity and recognition memory	Relatively insensitive to cognitive impairment	Lezak et al., 2004 (p. 849-850); Strauss et al., 2006
0	*Premorbid Functioning*[a]			
	1) North American Adult Reading Test (Strauss et al., 2006)	Premorbid intellectual ability	Inferior occipital-temporal cortex; inferior longitudinal fasciculus, and perisylvian language areas	Lezak et al., 2004 (p. 560); Strauss et al., 2006
	2) Word Reading (WRAT-4; Wilkinson & Robertson, 2006)	Premorbid intellectual ability	Inferior occipital-temporal cortex; inferior longitudinal fasciculus, and perisylvian language areas	Lezak et al., 2004 (p. 560); Strauss et al., 2006
I	*Attention/Working Memory*			

Table B.4 Cont.

#	Test Name	Cognitive Function	Hypothesized Localization(s)	Reference
	1) Arithmetic (WAIS III/IV) (Wechsler, 1997; Wechsler, 2008)	Mental Calculations and working memory	Left parietal lobe	Hom & Reitan, 1984; Lezak et al., 2004 (p. 605); McFie, 1975; Newcombe, 1969; Sivak et al., 1981
	2) Digit Span (WAIS III/IV) (Wechsler, 1997; Wechsler, 2008)	Verbal recall and auditory attention	Left hemisphere	Black, 1986; Hom & Reitan, 1984; Newcombe, 1969
	3) Animal Naming (Spreen & Strauss, 1998)	Word Fluency and Mental Flexibility	Left hemisphere; inferior temporal lobes; Broca's area; left medial occipital lobe	Damasio et al., 1996; Martin et al., 1996; Rosen, 1980
	4) Auditory Verbal Learning Test (AVLT) – Trial 1 (Rey, 1964)	Auditory working memory and immediate recall	Left hemisphere, left frontal, temporal, and parietal lobes	Geffen et al., 1990; Lezak et al., 2004; Powell et al., 1991
	5) Sentence Repetition (Spreen & Strauss, 1991)	Auditory comprehension, verbal expression, and articulation	Left hemisphere; middle cerebral artery infarcts; Broca's; Wernicke's; global aphasia	Goodglass & Kaplan, 1983; Lezak et al., 2004;
	6) Forced Choice (Brandt et al., 1985)	Verbal Expression	Left hemisphere	Lezak et al., 2004

Table B.4 Cont.

#	Test Name	Cognitive Function	Hypothesized Localization(s)	Reference
	7) Arithmetic (WRAT-4; Wilkinson & Robertson, 2006)	Written calculations	Left hemisphere; bilateral parietal lobes	Lezak et al., 2004 (p. 662)
	8) Paced Auditory Serial Addition Test (Gronwall, 1977; Gronwall & Sampson, 1974)	Attention, working memory, and information processing	Frontal and parietal lobes	Lazeron et al., 2003; Lezak et al., 2004 (p. 412); Strauss et al., 2006
	9) Minute Estimation (Meyers, 2019)	Attention	Frontal lobes	Meyers, 2019
	10) Dementia Rating Scale – 2 - Attention Index (Mattis, 2001)	Attention and working memory	Left hemisphere	Lezak et al., 2004 (p. 412); Strauss et al., 2006
	11) IVA-2 CPT – Auditory and Visual attention and sustained attention (Sandford & Turner, 1995)	Vigilance and sustained attention	Frontal lobes	Lezak et al., 2004 (p. 415-416); Tinius, 2003
II	*Processing Speed*			
	1) Digit Symbol/Coding (WAIS III/IV) (Wechsler, 1997; Wechsler, 2008)	Psychomotor speed and attention	[b]	Lezak et al., 2004 (p. 369)
	2) Trail Making Test – Part A (Reitan, 1958)	Attention, visual scanning, and over-learned sequencing	Frontal lobes	Reitan, 1958; Segalowitz et al., 1992
	3) Brake Pedal Test (Brake Reaction Test)	Psychomotor speed and attention	[b]	Hasegawa et al., 2020; Zhang et al., 2007
III	*Verbal Reasoning/Verbal Comprehension*			

Table B.4 Cont.

#	Test Name	Cognitive Function	Hypothesized Localization(s)	Reference
	1) Similarities (WAIS III/IV) (Wechsler, 1997; Wechsler, 2008)	Verbal abstraction	Left temporal and frontal lobes	Lezak et al., 2004 (p. 572); McFie, 1975; Newcombe, 1969; Warrington et al., 1986
	2) Information (WAIS III/IV) (Wechsler, 1997; Wechsler, 2008)	Long-term memory	Left hemisphere; general ability	Larrabee et al., 1985; Russell, 1987; Schoenberg et al., 2002; Sklar, 1963; Storandt et al., 1986
	3) Controlled Oral Word Association Test (Spreen & Strauss, 1998)	Mental flexibility and abstract reason	Left and right frontal	Ferret, 1974; Miceli et al., 1981; Rothi et al., 1991
	4) Boston Naming Test (Kaplan et al., 1983	Ability to name objects and language	Left hemisphere; Broca's area; hippocampus	Kaplan et al., 1983; Lezak et al., 2004; Margolin et al., 1990; Spreen & Strauss, 1998
	5) Token Test (Boller & Vignolo, 1966)	Receptive language, ability to follow directions and concentration	Left temporal and parietal	Boller & Vignolo, 1966; Strauss et al., 2006
	6) Dichotic Listening Test – Left sounds (Roberts et al., 1994)	Inter-hemispheric communication	Auditory system, ipsilateral and contra-lateral auditory system	Lezak et al., 2004; Meyers et al., 2002; Roberts et al., 1994

Table B.4 Cont.

#	Test Name	Cognitive Function	Hypothesized Localization(s)	Reference
	7) Dichotic Listening Test – Right sounds (Roberts et al., 1994)	Inter-hemispheric communication	Auditory system, more left contra-lateral auditory system than right	Lezak et al., 2004; Meyers et al., 2002; Roberts et al., 1994
	8) Spelling (WRAT-4; Wilkinson & Robertson, 2006)	Expressive language and lexical comprehension	Left hemisphere; general ability	Lezak et al., 2004 (p. 564-565)
	9) Dementia Rating Scale – 2 – Conceptualization Index (Mattis, 2001)	Verbal abstraction and reasoning	Left temporal and frontal lobes	Lezak et al., 2004 (p. 412); Strauss et al., 2006
IV	*Visual Reasoning/Perceptual Organization*			
	1) Picture Completion (WAIS III/IV) (Wechsler, 1997; Wechsler, 2008)	Visual spatial perceptual skills and discrimination of essential and non-essential details	Right parietal, temporal, and occipital lobes	Chase et al., 1984; Lezak et al., 2004 (p. 598)
	2) Block Design (WAIS III/IV) (Wechsler, 1997; Wechsler, 2008)	Visual spatial organization	Right posterior and left parietal lobes	Black & Strub, 1976; Lezak et al., 2004 (p. 560); McFie, 1975; Newcombe, 1969; Warrington et al., 1986
	3) Judgement of Line Orientation (Benton et al., 1983b)	Ability to perceive visual information and judge lines and angles	Right posterior parietal and anterior occipital lobes	Benton et al., 1983b; Tranel et al., 2009
	4) Rey Complex Figure Test – Copy (Rey, 1964)	Visual Organization	Right hemisphere; parietal and temporal	Meyers & Meyers, 1995

Table B.4 Cont.

#	Test Name	Cognitive Function	Hypothesized Localization(s)	Reference
	5) Dementia Rating Scale – 2 – Construction Index (Mattis, 2001)	Visual-perceptual/visual-constructional	Subcorticial hyperintensities	Lezak et al., 2004 (p. 412); Strauss et al., 2006
V	*Verbal Memory/Auditory Memory and Learning*			
	1) Rey Auditory Verbal Learning Test – Total learning trials, immediate recall, delayed recall, and recognition (Rey, 1964)	Learning, immediate and delayed free recall, and recognition of verbal information	Left hemisphere	Lezak et al., 2004; Geffen et al., 1990
	2) Dementia Rating Scale – 2 – Memory Index (Mattis, 2001)	Learning, immediate and delayed free recall, and recognition	Hippocampus	Lezak et al., 2004 (p. 412); Strauss et al., 2006
	3) Wide Range Assessment of Memory and Learning – 2 Immediate recall, delayed recall and recognition Story Memory (Sheslow & Adams, 2003)	Immediate and delayed free recall, and recognition	Left hemisphere; hippocampus	Lezak et al., 2004 (p. 536); Strauss et al., 2006
VI	*Visual Memory/Nonverbal Memory and Learning*			
	1) Rey Complex Figure Test – immediate recall, delayed recall, and recognition (Rey, 1964)	Visual Organization, immediate and delayed recall of visual information	Right hemisphere	Meyers & Meyers, 1995
VII	*Executive Functioning*			

Table B.4 Cont.

#	Test Name	Cognitive Function	Hypothesized Localization(s)	Reference
	1) Trail Making Test – Part B (Reitan, 1958)	Attention, set switching, eye-hand coordination, working memory	Frontal lobes	Greenlief et al., 1985; Reitan & Wolfson, 1985; Ruffolo et al., 2000; Segalowitz et al., 1992
	2) Dichotic Listening Test– Both Left and Right Sounds (Meyers et al., 2002)	Bilateral inter-hemispheric communication	Auditory system, more left contra-lateral auditory system than right	Meyers et al., 2002; Lezak et al., 2004; Roberts et al., 1994
	3) Category Test (Spreen & Strauss, 1991)	Problem solving and reasoning abilities	Right hemisphere	Cullum & Bigler, 1986; Goldstein & Ruthven, 1983; Halstead, 1947; King & Snow, 1981; Wang, 1987
	4) Wisconsin Card Sorting Test – percent errors, perseverative responses, and perseverative errors (Berg, 1948)	Problem solving, set-shifting, mental flexibility, judgement	Frontal lobes, dorsolateral prefrontal	Lezak et al., 2004 (p. 637-639)
	5) Dementia Rating Scale – 2 – Initiation/Perseveration Index (Mattis, 2001)	Inhibitory control and mental flexibility	Frontal lobes, subcortical hyperintensities	Lezak et al., 2004 (p. 412); Strauss et al., 2006
	6) IVA-2 CPT – Auditory and Visual Response Control (Sandford & Turner, 1995)	Inhibitory control/response inhibition	Frontal lobes	Lezak et al., 2004 (p. 415-16); Tinius, 2003
VIII	*Dominant Motor and Sensory*			

Table B.4 Cont.

#	Test Name	Cognitive Function	Hypothesized Localization(s)	Reference
	1) Finger Tapping Test – Dominant (Reitan & Wolfson, 1985)	Motor speed and persistence	Contralateral and ipsilateral motor, contralateral premotor, contralateral dorsolateral prefrontal, and ipsilateral cerebellum	Lezak et al., 2012; Prigatano et al., 2004; Strauss et al., 2006
	2) Finger Localization Test – Dominant (Benton et al., 1983b)	Tactile identification	Left posterior perisylvian region; right hemisphere	Benton et al., 1983b; Gainotti, & Tiacci, 1973
	3) Grooved Pegboard Test – Dominant (Matthews & Klove, 1964)	Motor Speed and Fine Motor Dexterity	Contralateral and ipsilateral motor cortex	Lezak et al., 2012; Strauss et al., 2006
IX	*Non-Dominant Motor and Sensory*			
	1) Finger Tapping Test – Non-Dominant (Reitan & Wolfson, 1985)	Motor speed and persistence	contralateral and ipsilateral motor, contralateral premotor, contralateral dorsolateral prefrontal, and ipsilateral cerebellum	Lezak et al., 2012; Prigatano et al., 2004; Strauss et al., 2006

Table B.4 Cont.

#	Test Name	Cognitive Function	Hypothesized Localization(s)	#
	2) Finger Localization Test – Non-Dominant (Benton et al., 1983b)	Tactile identification	Left posterior perisylvian region; right hemisphere	Benton et al., 1983b; Gainotti, & Tiacci, 1973
	3) Grooved Pegboard Test – Non-Dominant (Matthews & Klove, 1964)	Motor Speed and Fine Motor Dexterity	Contralateral and ipsilateral motor cortex	Lezak et al., 2012; Strauss et al., 2006

Note. Adapted from Meyers and Rohling (2009). [a] = tests from this domain were not included in calculations of OTBM or IIV. [b] = very sensitive to brain damage and depressed regardless of location of the locus of a lesion. WRAT = Wide Range Achievement Test. WAIS = Wechsler Adult Intelligence Scale. Integrated Visual and Auditory = IVA. Continuous Performance Test = CPT.

Table B.5

Bivariate Correlations between Cognitive Variables

	2	3	4	5	6	7	8	9	10	11	12	13
1) OTBM	-.45***	-.27***	.54***	.77***	.72***	.75***	.69***	.77***	.68***	.76***	.52***	.44***
2) IIV		-.20***	<-.01	-.35***	-.45***	-.21***	-.15***	-.31***	-.34***	-.26***	-.39***	-.30***
3) PVTs Failed			-.07	-.21***	-.13**	-.11*	-.14***	-.38***	-.20***	-.11*	-.10*	-.08
4) Premorbid Est.				.41***	.23***	.66***	.54***	.36***	.31***	.50***	.12**	.13**
5) Attention/WM					.53***	.55***	.42***	.45***	.39***	.56***	.34***	.23***
6) Processing Speed						.46***	.36***	.29***	.39***	.55***	.45***	.33***
7) Verbal Reasoning							.48***	.43***	.34***	.64***	.24***	.17***
8) Visual Reasoning								.36***	.58***	.66***	.30***	.28***
9) Verbal Memory									.43***	.40***	.22***	.19***
10) Visual Memory										.49***	.30***	.31***
11) EF											.34***	.28***
12) Dom Motor												.59***
13) NonDom Motor												

Note. OTBM = Overall Test Battery Mean. IIV = Intra-Individual Variability. PVT = Performance Validity Test. Est. = Estimate. WM = Working Memory. EF = Executive Functioning. Dom Motor = Dominant Motor Functioning. NonDom Motor = Non-Dominant Motor Functioning.

* < .05. **<.01. ***<.001.

N = 497.

Table B.6

Bivariate Correlations between Sample Diagnoses and OTBM and IIV

	OTBM	IIV
Internalizing	.02	-.02
Impulse Control	.02	-.02
Substance Abuse	<-.01	.01
Years of Substance Abuse	-.02	-.05
Severe Mental Illness	.05	.01
Learning	.09	.04
Neurodevelopmental	.17***	-.06
Seizure	.03	-.08
Neurocognitive	.10*	-.05
Chiari Malformation	-.02	.06
Brain Tumor	<.01	-.07
All Types of Traumatic Brain Injury	.03	.02
Post Concussive Syndrome	.09	-.02
Mild TBI	-.03	.12*
Moderate to Severe TBI	.14**	-.14**
Cardiovascular	.16**	-.21***
Hyperlipidemia	-.06	.04
Autoimmune	.05	-.11*
Hyperchloremia	-.02	-.04
Respiratory Dysfunction	-.12**	-.05
Pain	-.09	.12**
Migraine	-.03	-.03
Tinnitus	-.02	<.01
Eating Disorders	.01	-.04
Sleep Dysfunction	<-.01	.05

Note. N = 497. * < .05. **<.01. ***<.001.

Table B.7

Bivariate Correlations between Therapeutic Use Categories and OTBM and IIV

	OTBM	IIV
Polypharmacy	.03	-.06
Anticholinergic	.06	-.02
Antidepressant	.01	-.04
Anxiolytic	.07	-.05
Antipsychotic	.10**	-.05
Mood Stabilizer	.06	-.05
Analgesic	.07	-.07
Addiction	.06	-.05
Antiepileptic	.11**	-.08
Stimulant	.05	-.05
Antidementia	.06	-.05
Cardiovascular	.07	-.06
Lipid Modifying	.04	-.04
Antithrombotic	.08	-.07
Anti-inflammatory	.01	<.01
Hormone	.03	-.01
Respiratory	.08	-.03
Antidiabetic	.10**	-.05
Antihistamine	.07	-.06
Urological	.05	-.05
Gastrointestinal	.05	-.03
Muscle Relaxants	.06	-.06
Calcium and Bone Mineralization	.06	-.05
Immunomodulator	.06	-.06
Movement Disorder	.05	-.04
Antiglaucoma	.06	-.05
Dermatological	.06	-.06
Antimalarial	.06	-.04
Cytotoxic	.06	-.05
Weight Loss	.06	-.05
Antigout	.06	-.04

Note. N = 497. * < .05. **<.01. ***<.001

Table B.8

Bivariate Correlations between Demographic Variables and OTBM and IIV

	OTBM	IIV
Age	.15**	-.05
Gender	.04	.01
Ethnicity	-.02	-.05
Neuropsychologist	-.03	.33***

Note. N = 497. * < .05. **<.01. ***<.001

Table B.9

Bivariate Correlations between Sample Diagnoses and Cognitive Domains

	Premorbid Est.	Attn/ WM	PS	Verbal Reasoning	Visual Reasoning	Verbal Memory	Visual Memory	EF	Dom Motor	Non-Dom Motor
Internalizing	-.05	.05	-.01	-.09	.07	-.02	.07	.01	.08	.01
Impulse Control	-.01	.02	<-.01	-.01	.01	.08	.01	<.01	.04	.01
SA	.07	<.01	-.03	.02	<-.01	.03	.04	-.01	-.07	-.02
Years of SA	-.05	<.01	.06	<-.01	-.06	-.02	-.05	-.02	.05	.01
SMI	.06	.04	<.01	.06	.07	.09	.06	.05	-.02	<.01
Learning	.18**	.12*	.02	.13**	.08	<.01	.01	.09	-.09	-.10*
Neurodevelopmental	.29***	.12*	.01	.21***	.20***	.09	.10*	.17***	.10	.09
Seizure	-.01	.06	.04	.02	.01	-.01	<.01	-.01	-.01	.02
Neurocognitive	-.09	.03	.09	.01	.02	.11*	.12*	.06	.11*	.14**
Chiari Malformation	-.03	.03	-.02	<.01	.01	-.03	<.01	-.02	<.01	.03
Brain Tumor	<-.01	-.04	.04	.03	-.02	<.01	-.01	-.02	-.02	.01
All Types of TBI	.03	-.01	.10*	.11*	-.04	.08	-.04	.02	-.04	-.04
PCS	.03	.07	.11*	.09	-.01	.11*	.09	.03	.02	.05
Mild TBI	.03	-.06	.02	.06	-.03	<-.01	-.07	.02	-.08	-.08
Mod. to Severe TBI	.03	.10*	.16**	.12*	.01	.17***	.05	.04	.08	.08
Cardiovascular	-.04	.11*	.16**	.07	.09	.06	.10*	.11*	.22***	.19***
Hyperlipidemia	-1.3*	-.02	-.06	-.06	-.07	-.04	-.07	-.05	.11*	.16**
Autoimmune	-1.2*	.10	.03	-.08	-.04	-.03	.01	.06	.17**	.11*
Hyperchloremia	-.09	.02	.02	-.04	-.02	-.09	-.04	.04	.12*	<-.01
Respiratory Disorder	-.17***	-.07	-.12*	-.14**	-.15*	-.07	-.04	-.01	<.01	-.03
Pain	.04	-.05	-.15**	<.01	<-.01	-.06	-.06	-.05	-.09	-.03
Migraine	-.02	.03	.04	-.04	-.04	-.04	.05	-.02	-.05	-.11*

Table B.9 Cont.

	Premorbid Est.	Attn/ WM	PS	Verbal Reasoning	Visual Reasoning	Verbal Memory	Visual Memory	EF	Dom Motor	Non-Dom Motor
Tinnitus	-.09	-.02	-.01	-.05	.01	-.02	-.05	.06	-.04	-.05
Eating Disorder	-.06	-.07	.05	-.02	.02	-.03	.04	.03	.06	.06
Sleep Disorder	-.06	.02	.04	<-.01	.03	<.01	.03	-.01	-.05	-.09

Note. N = 497. SA = Substance Abuse. SMI = Severe Mental Illness. TBI = Traumatic Brain Injury. PCS = Post Concussive Syndrome. Mod. = Moderate. Dis. = Disorder. Est. = Estimate. Attn/WM = Attention/Working Memory. PS = Processing Speed. EF = Executive Functioning. Dom Motor = Dominant Motor Functioning. Non-Dom Motor = Non-Dominant Motor Functioning.
* < .05. **<.01. ***<.001.

Table B.10

Bivariate Correlations between Therapeutic Use Categories and Cognitive Domains

	Premorbid Est.	Attn/WM	PS	Verbal Reasoning	Visual Reasoning	Verbal Memory	Visual Memory	EF	Dom Motor	Non-Dom Motor
Polypharmacy	.05	.01	.05	.07	-.02	.02	-.03	-.03	-.09	-.09
Anticholinergics	.05	.05	.07	.05	.03	.02	.04	-.02	-.02	.01
Antidepressants	<-.01	.02	.01	-.01	<.01	-.02	.01	-.08	-.02	<-.01
Anxiolytics	.06	.07	.06	.08	.03	.07	.02	<-.01	-.01	-.02
Antipsychotics	.11*	.08	.09*	.11*	.06	.07	.07	.03	-.02	-.01
Mood Stabilizers	.06	.04	.08	.08	<.01	.04	.01	-.02	-.03	-.04
Analgesics	.05	.06	.06	.07	.03	.04	.03	-.01	-.01	.03
Addiction	.07	.04	.08	.08	.01	.04	.01	-.01	-.04	-.05
Antiepileptics	.10*	.09*	.16***	.13**	.02	.06	.01	.04	.02	.01
Stimulants	.05	.02	.09*	.07	.01	.01	<.01	-.02	-.03	-.05
Antidementia	.05	.05	.08	.08	<.01	.04	<.01	-.01	-.02	-.04
Cardiovascular	.04	.03	.08	.07	.01	.08	.02	<.01	<.01	.01
Lipid Modifying	.03	.02	.07	.06	.01	.02	.01	-.02	-.03	-.02
Antithrombotic	.07	.05	.10*	.10*	.02	.05	.02	<.01	<.01	-.03
Anti-inflammatory	.08	-.01	.03	.06	<-.01	<-.01	-.01	-.03	-.06	-.02
Hormones	.02	.05	.03	.04	-.01	.03	<-.01	-.02	-.02	-.05
Respiratory	.09	.06	.09	.09*	.01	.04	.02	.02	-.02	-.03
Antidiabetics	.08	.08	.10*	.11*	.03	.06	.03	.05	-.01	-.02
Antihistamines	.05	.06	.09	.07	<.01	.04	.04	-.02	-.01	-.01
Urological	.06	.03	.07	.08	.01	.02	<.01	-.01	-.04	-.02
Gastrointestinal	.05	.04	.08	.07	.01	-.01	.02	-.01	-.02	.02
Muscle Relaxants	.07	.05	.08	.09	<.01	.04	<-.01	-.02	-.02	-.03

Table B.10 Cont.

	Premorbid Est.	Attn/WM	PS	Verbal Reasoning	Visual Reasoning	Verbal Memory	Visual Memory	EF	Dom Motor	Non-Dom Motor
Calcium & Bone Mineralization	.05	.03	.09*	.08	.01	.03	.01	-.01	-.03	-.03
Immunomodulators	.06	.05	.09*	.09	.01	.03	.01	-.01	-.02	-.03
Movement Disorder	.06	.04	.07	.08	<-.01	.04	<.01	-.02	-.03	-.04
Antiglaucoma	.06	.05	.08	.09	.01	.04	.01	-.01	-.03	-.04
Dermatological	.06	.04	.08	.09	.01	.03	.01	-.01	-.03	-.04
Antimalarial	.06	.04	.08	.09	.01	.04	.01	-.01	-.04	-.04
Cytotoxic	.06	.04	.08	.08	<-.01	.04	.01	-.02	-.03	-.04
Weight Loss	.06	.04	.08	.08	.01	.03	.01	-.01	-.03	-.04
Antigout	.06	.05	.08	.08	.01	.04	.01	-.01	-.03	-.04

Note: N = 497. Est. = Estimate. Attn/WM = Attention/Working Memory. PS = Processing Speed. EF = Executive Functioning. Dom Motor = Dominant Motor Functioning. Non-Dom Motor = Non-Dominant Motor Functioning.
* < .05. **<.01. ***<.001.

Table B.11

Bivariate Correlations between Demographic Variables and Cognitive Domains

	Premorbid Est.	Attn/WM	PS	Verbal Reasoning	Visual Reasoning	Verbal Memory	Visual Memory	EF	Dom Motor	Non-Dom Motor
Age	.14**	.14**	.18***	.15***	.09*	.01	.08	.08	.02	-.09*
Gender	.03	.12**	-.08	.03	.08	.02	.07	.05	-.03	-.04
Ethnicity	-.05	-.07	.01	-.02	-.02	-.01	-.02	<.01	.09	.07
Neuropsychologist	.34***	-.15***	-.19***	.24***	.11**	.12**	-.03	<-.01	-.16***	-.07

Note: N = 497. Est. = Estimate. Attn/WM = Attention/Working Memory. PS = Processing Speed. EF = Executive Functioning. Dom Motor = Dominant Motor Functioning. NonDom Motor = Non-Dominant Motor Functioning.

* < .05. **<.01. ***<.001.

Appendix C – ANCOVA Tables

Table C.1

Interaction and Main Effects of 3x3 ANCOVA of Effects of Anticholinergic Medication Use and Polypharmacy on OTBM

		Polypharmacy								
		Polypharmacy (n = 46)		No Polypharmacy (n = 277)		No Meds (n = 65)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
OTBM	Yes (n = 77)	43.18	5.88	45.20	5.16	-	-	Anticholinergics	0.45	< .01
	No (n = 246)	44.48	6.18	44.22	5.79	-	-	Polypharmacy	0.25	< .01
	No Meds (n = 65)	-	-	-	-	43.86	4.66	Anticholinergic x Polypharm	3.65	< .01

Note. N = 497. OTBM = Overall Test Battery Mean. Estimated premorbid functioning, age, location of evaluation; use of anxiolytics, AEDs, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.
*p<.006. **p<.001.

Table C.2

Interaction and Main Effects of 3x3 ANCOVA of Effects of Anticholinergic Medication Use and Polypharmacy on IIV

		Polypharmacy								
		Polypharmacy (n = 44)		No Polypharmacy (n = 271)		No Meds (n = 63)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
IIV	Yes (n = 75)	10.04	2.96	9.38	2.39	-	-	Anticholinergics	0.65	< .01
	No (n = 240)	9.34	2.22	9.86	2.42	-	-	Polypharmacy	0.88	.01
	No Meds (n = 63)	-	-	-	-	10.03	2.73	Anticholinergic x Polypharm	3.82	< .01

Note. N = 497. IIV = Intra-Individual Variability. Estimated premorbid functioning, age, location of evaluation; use of anxiolytics, AEDs, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.

*p<.006. **p<.001.

Table C.3

Interaction and Main Effects of 3x3 ANCOVA of Effects of Antidepressant Medication Use and Polypharmacy on OTBM

		Polypharmacy								
		Polypharmacy (n = 46)		No Polypharmacy (n = 277)		No Meds (n = 65)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
OTBM	Yes (n = 180)	44.21	5.64	45.02	5.64	-	-	Antidepressant	0.80	< .01
	No (n = 143)	43.00	8.07	43.81	5.65	-	-	Polypharmacy	0.04	< .01
	No Meds (n = 65)	-	-	-	-	43.86	4.66	Antidepressant x Polypharm	0.09	< .01

Note. N = 497. OTBM = Overall Test Battery Mean. Estimated premorbid functioning, age, location of evaluation; use of anxiolytics, antipsychotics, analgesics, AEDs, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.

*p<.006. **p<.001.

Table C.4

Interaction and Main Effects of 3x3 ANCOVA of Effects of Antidepressant Medication Use and Polypharmacy on IIV

		Polypharmacy								
		Polypharmacy (n = 44)		No Polypharmacy (n = 271)		No Meds (n = 63)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
IIV	Yes (n = 175)	9.62	2.69	9.70	2.39	-	-	Antidepressant	0.18	< .01
	No (n = 140)	9.56	1.68	9.82	2.46	-	-	Polypharmacy	5.29	0.01
	No Meds (n = 63)	-	-	-	-	10.03	2.73	Antidepressant x Polypharm	<0.01	< .01

Note. N = 497. IIV = Intra-Individual Variability. Estimated premorbid functioning, age, location of evaluation; use of, anxiolytics, antipsychotics, analgesics, AEDs, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.
*p<.006. **p<.001.

Table C.5

Interaction and Main Effects of 3x3 ANCOVA of Effects of Anxiolytic Medication Use and Polypharmacy on OTBM

		Polypharmacy								
		Polypharmacy (n = 46)		No Polypharmacy (n = 277)		No Meds (n = 65)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
OTBM	Yes (n = 55)	43.05	5.39	44.48	6.78	-	-	Anxiolytics	1.99	< .01
	No (n = 268)	44.88	6.57	44.43	5.52	-	-	Polypharmacy	0.03	< .01
	No Meds (n = 65)	-	-	-	-	43.86	4.66	Anxiolytics x Polypharm	6.48	< .01

Note. N = 497. OTBM = Overall Test Battery Mean. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, antipsychotics, analgesics, AEDs, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.

*p<.006. **p<.001.

Table C.6

Interaction and Main Effects of 3x3 ANCOVA of Effects of Anxiolytic Medication Use and Polypharmacy on IIV

		Polypharmacy								
		Polypharmacy (n = 44)		No Polypharmacy (n = 271)		No Meds (n = 63)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
IIV	Yes (n = 54)	10.12	2.37	9.62	2.71	-	-	Anxiolytic	1.79	< .01
	No (n = 261)	9.10	2.62	9.78	2.38	-	-	Polypharmacy	4.47	< .01
	No Meds (n = 63)	-	-	-	-	10.03	2.73	Anxiolytic x Polypharm	4.76	.01

Note. N = 497. IIV = Intra-Individual Variability. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, antipsychotics, analgesics, AEDs, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.

*p<.006. **p<.001.

Table C.7

Interaction and Main Effects of 3x3 ANCOVA of Effects of Analgesic Medication Use and Polypharmacy on OTBM

		Polypharmacy								
		Polypharmacy (n = 46)		No Polypharmacy (n = 277)		No Meds (n = 65)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
OTBM	Yes (n = 53)	42.41	6.65	44.97	7.61	-	-	Analgesic	3.97	< .01
	No (n = 270)	45.46	5.14	44.37	5.39	-	-	Polypharmacy	< 0.01	< .01
	No Meds (n = 65)	-	-	-	-	43.86	4.66	Analgesic x Polypharm	2.00	< .01

Note. N = 497. OTBM = Overall Test Battery Mean. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, anxiolytics, antipsychotics, AEDs, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.

*p<.005. **p<.001.

Table C.8

Interaction and Main Effects of 3x3 ANCOVA of Effects of Analgesic Medication Use and Polypharmacy on IIV

		Polypharmacy								
		Polypharmacy (n = 44)		No Polypharmacy (n = 271)		No Meds (n = 63)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
IIV	Yes (n = 51)	10.40	2.68	9.95	2.79	-	-	Analgesic	11.29	.02**
	No (n = 264)	8.89	2.19	9.73	2.38	-	-	Polypharmacy	4.65	.01
	No Meds (n = 63)	-	-	-	-	10.03	2.73	Analgesic x Polypharm	2.89	< .01

Note. N = 497. IIV = Intra-Individual Variability. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, anxiolytics, antipsychotics, AEDs, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.

*p<.005. **p<.001.

Table C.9

Interaction and Main Effects of 3x3 ANCOVA of Effects of Using Triptans and Polypharmacy on IIV

		Polypharmacy								
		Polypharmacy (n = 44)		No Polypharmacy (n = 271)		No Meds (n = 63)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
IIV	Yes (n = 6)	12.08	3.03	12.70	3.96	-	-	Triptans	12.91	.03**
	No (n = 309)	9.36	2.37	9.74	2.40	-	-	Polypharmacy	2.79	< .01
	No Meds (n = 63)	-	-	-	-	10.03	2.73	Triptans x Polypharm	0.44	< .01

Note. N = 497. IIV = Intra-Individual Variability. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, anxiolytics, antipsychotics, AEDs, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.

*p<.005. **p<.001.

Table C.10

Interaction and Main Effects of 3x3 ANCOVA of Effects of Using Opioid Analgesics and Polypharmacy on IIV

		Polypharmacy								
		Polypharmacy (n = 44)		No Polypharmacy (n = 271)		No Meds (n = 63)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
IIV	Yes (n = 27)	9.65	2.07	9.55	2.23	-	-	Opioids	0.10	< .01
	No (n = 288)	9.60	2.68	9.77	2.43	-	-	Polypharmacy	1.87	< .01
	No Meds (n = 63)	-	-	-	-	10.03	2.73	Opioids x Polypharm	0.07	< .01

Note. N = 497. IIV = Intra-Individual Variability. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, anxiolytics, antipsychotics, AEDs, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.

*p<.005. **p<.001.

Table C.11

Interaction and Main Effects of 3x3 ANCOVA of Effects of Using Opioid-Combination Analgesics and Polypharmacy on IIV

		Polypharmacy								
		Polypharmacy (n = 44)		No Polypharmacy (n = 271)		No Meds (n = 63)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
IIV	Yes (n = 14)	10.75	1.97	10.44	3.99	-	-	Opioid-Combinations	2.13	< .01
	No (n = 301)	9.43	2.57	9.74	2.36	-	-	Polypharmacy	1.70	< .01
	No Meds (n = 63)	-	-	-	-	10.03	2.73	Opioid Combos x Polypharm	<0.01	< .01

Note. N = 497. IIV = Intra-Individual Variability. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, anxiolytics, antipsychotics, AEDs, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.

*p<.005. **p<.001.

Table C.12

Interaction and Main Effects of 3x3 ANCOVA of Effects of Using Non-Opioid Analgesics and Polypharmacy on IIV

		Polypharmacy								
		Polypharmacy (n = 44)		No Polypharmacy (n = 271)		No Meds (n = 63)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
IIV	Yes (n = 10)	10.90	3.93	8.76	1.22	-	-	Non-Opioids	0.20	< .01
	No (n = 305)	9.44	2.31	9.78	2.43	-	-	Polypharmacy	0.01	< .01
	No Meds (n = 63)	-	-	-	-	10.03	2.73	Non-Opioids x Polypharm	1.48	< .01

Note. N = 497. IIV = Intra-Individual Variability. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, anxiolytics, antipsychotics, AEDs, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.

*p<.005. **p<.001.

Table C.13

Interaction and Main Effects of 3x3 ANCOVA of Effects of Antiepileptic Medication Use and Polypharmacy on OTBM

		Polypharmacy								
		Polypharmacy (n = 46)		No Polypharmacy (n = 277)		No Meds (n = 65)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
OTBM	Yes (n = 76)	45.62	4.95	42.43	5.87	-	-	Antiepileptic	3.41	< .01
	No (n = 247)	43.13	6.46	44.99	5.50	-	-	Polypharmacy	0.88	< .01
	No Meds (n = 65)	-	-	-	-	43.86	4.66	Antiepileptic x Polypharm	4.51	< .01

Note. N = 497. OTBM = Overall Test Battery Mean. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, anxiolytics, antipsychotics, analgesics, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.

*p<.006. **p<.001.

Table C.14

Interaction and Main Effects of 3x3 ANCOVA of Effects of Antiepileptic Medication Use and Polypharmacy on IIV

		Polypharmacy								
		Polypharmacy (n = 44)		No Polypharmacy (n = 271)		No Meds (n = 63)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
IIV	Yes (n = 74)	9.13	1.96	10.47	2.41	-	-	Antiepileptic	1.83	< .01
	No (n = 241)	9.86	2.76	9.56	2.39	-	-	Polypharmacy	9.56	0.02*
	No Meds (n = 63)	-	-	-	-	10.03	2.73	Antiepileptic x Polypharm	4.79	.01

Note. N = 497. IIV = Intra-Individual Variability. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, anxiolytics, antipsychotics, analgesics, cardiovascular medications, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.

*p<.006. **p<.001.

Table C.15

Interaction and Main Effects of 3x3 ANCOVA of Effects of Cardiovascular Medication Use and Polypharmacy on OTBM

		Polypharmacy								
		Polypharmacy (n = 46)		No Polypharmacy (n = 277)		No Meds (n = 65)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
OTBM	Yes (n = 72)	43.08	6.43	43.69	5.61	-	-	Cardiovascular	2.48	< .01
	No (n = 251)	45.00	5.56	44.59	5.68	-	-	Polypharmacy	0.13	< .01
	No Meds (n = 65)	-	-	-	-	43.86	4.66	Cardiovascular x Polypharm	0.53	< .01

Note. N = 497. OTBM = Overall Test Battery Mean. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, anxiolytics, antipsychotics, analgesics, AEDs, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.
*p<.006. **p<.001.

Table C.16

Interaction and Main Effects of 3x3 ANCOVA of Effects of Cardiovascular Medication Use and Polypharmacy on IIV

		Polypharmacy								
		Polypharmacy (n = 44)		No Polypharmacy (n = 271)		No Meds (n = 63)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
IIV	Yes (n = 69)	9.86	2.97	10.04	2.30	-	-	Cardiovascular	0.01	< .01
	No (n = 246)	9.34	1.95	9.70	2.44	-	-	Polypharmacy	6.76	0.01
	No Meds (n = 63)	-	-	-	-	10.03	2.73	Cardiovascular x Polypharm	0.23	< .01

Note. N = 497. IIV = Intra-Individual Variability. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, anxiolytics, antipsychotics, analgesics, AEDs, anti-inflammatory medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.
*p<.006. **p<.001.

Table C.17

Interaction and Main Effects of 3x3 ANCOVA of Effects of Anti-Inflammatory Medication Use and Polypharmacy on OTBM

		Polypharmacy								
		Polypharmacy (n = 46)		No Polypharmacy (n = 277)		No Meds (n = 65)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
OTBM	Yes (n = 63)	44.24	6.06	45.60	5.41	-	-	Anti-Inflammatory	3.19	< .01
	No (n = 260)	43.80	6.14	44.23	5.70	-	-	Polypharmacy	0.18	< .01
	No Meds (n = 65)	-	-	-	-	43.86	4.66	Anti-Inflammatory x Polypharm	0.03	< .01

Note. N = 497. OTBM = Overall Test Battery Mean. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, anxiolytics, antipsychotics, analgesics, AEDs, cardiovascular medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.
*p<.006. **p<.001.

Table C.18

Interaction and Main Effects of 3x3 ANCOVA of Effects of Anti-Inflammatory Medication Use and Polypharmacy on IIV

		Polypharmacy								
		Polypharmacy (n = 44)		No Polypharmacy (n = 271)		No Meds (n = 63)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
IIV	Yes (n = 61)	9.43	2.48	9.15	2.23	-	-	Anti-Inflammatory	0.34	< .01
	No (n = 254)	9.75	2.59	9.87	2.44	-	-	Polypharmacy	5.77	0.01
	No Meds (n = 63)	-	-	-	-	10.03	2.73	Anti-Inflammatory x Polypharm	0.29	< .01

Note. N = 497. IIV = Intra-Individual Variability. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, anxiolytics, antipsychotics, analgesics, AEDs, cardiovascular medications, and hormones; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.
*p<.006. **p<.001.

Table C.19

Interaction and Main Effects of 3x3 ANCOVA of Effects of Hormone Medication Use and Polypharmacy on OTBM

		Polypharmacy								
		Polypharmacy (n = 46)		No Polypharmacy (n = 277)		No Meds (n = 65)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
OTBM	Yes (n = 61)	44.88	5.12	45.09	5.53	-	-	Hormone	0.09	< .01
	No (n = 262)	43.53	6.51	44.31	5.70	-	-	Polypharmacy	0.26	< .01
	No Meds (n = 65)	-	-	-	-	43.86	4.66	Hormone x Polypharm	0.23	< .01

Note. N = 497. OTBM = Overall Test Battery Mean. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, anxiolytics, antipsychotics, analgesics, AEDs, cardiovascular medications, and anti-inflammatory medications; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.

*p<.006. **p<.001.

Table C.20

Interaction and Main Effects of 3x3 ANCOVA of Effects of Anti-Inflammatory Medication Use and Polypharmacy on IIV

		Polypharmacy								
		Polypharmacy (n = 44)		No Polypharmacy (n = 271)		No Meds (n = 63)				
		M	*SD*	*M*	*SD*	*M*	*SD*	Factors	*F*	η^2
IIV	Yes (n = 60)	9.60	3.15	9.22	2.86	-	-	Anti-Inflammatory	1.13	< .01
	No (n = 255)	9.61	2.15	9.86	2.43	-	-	Polypharmacy	6.76	0.01
	No Meds (n = 63)	-	-	-	-	10.03	2.73	Anti-Inflammatory x Polypharm	0.18	< .01

Note. N = 497. IIV = Intra-Individual Variability. Estimated premorbid functioning, age, location of evaluation; use of antidepressants, anxiolytics, antipsychotics, analgesics, AEDs, cardiovascular medications, and anti-inflammatory medications; and diagnoses of internalizing disorders, substance abuse, SMI, learning disorders, neurodevelopmental disorders, seizure disorders, neurocognitive disorders, moderate to severe TBI, cardiovascular diagnoses, respiratory disorders, and pain were included as covariates.

*p<.006. **p<.001.

BIOGRAPHICAL SKETCH

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Name of Author: Sarah E. Taylor

Graduate and Undergraduate Schools Attended:

University of South Alabama Mobile, Alabama
James Madison University Harrisonburg, Virginia

Degrees Awarded:

Doctor of Philosophy in Clinical Psychology Expected December 2021, Mobile, Alabama
Master of Science in Psychology 2019, Mobile, Alabama
Bachelor of Science in Psychology and a minor in Biology 2013, Harrisonburg, Virginia