EXECUTIVE FUNCTION, COGNITIVE IMPAIRMENT, ILLNESS PERCEPTIONS AND MEDICATION ADHERENCE AMONG HEART TRANSPLANT RECIPIENTS

by

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DEDICATION

I dedicate this accomplishment to my husband, Hob. Your love and support have made this possible. Thank you for always being in my corner!

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ABSTRACT

Heart transplant recipients are required to take lifelong immunosuppression medications to prevent organ rejection and preserve organ function, however rates of medication nonadherence remain high. This population is at an increased cumulative risk for cerebral hypoxic injury over the course of their lifetime, and a substantial portion of heart transplant recipients may be at risk for cognitive impairment for these reasons. While evidence indicates that a relationship between certain cognitive processes (e.g., executive function) and medication adherence exists across a wide range of chronic diseases, the relationship between these variables has not been studied in heart transplant recipients. The purpose of this research was to describe the associations between certain types of cognitive processes, illness perceptions, and medication adherence in heart transplant recipients. A cross-sectional, observational study involving 35 heart transplant recipients examined these associations. Findings indicate that episodic memory, intrusions, and cognitive impairment were related to medication adherence in this sample. Additionally, illness coherence and depression were associated with adherence. Findings from this study support the need for longitudinal evaluations of cognitive function, depression, and medication adherence and should be considered when developing interventions to support medication adherence.

CHAPTER I: INTRODUCTION

Heart transplantation is a valuable treatment option that is known to improve longevity and quality of life for individuals with end-stage heart failure (McCurry, 2019; Riether et al., 1992). Heart transplantation represents the treatment of choice for individuals with end-stage heart failure when symptoms and underlying disease pathology are not improved with medical therapies or other surgical alternatives (Alraies & Eckman, 2014). There is a disparity between the need for heart transplantation and the availability of donor organs. This disparity mandates that transplant centers identify individuals who are most likely to benefit through an extensive pre-transplantation medical, surgical, and psychosocial evaluation (Alraies & Eckman, 2014; McCurry, 2019). The individual's capacity to participate in decision-making, previous treatment adherence, coping skills, medication affordability, and knowledge and understanding of treatment options are involved in this evaluation (Dew et al., 2019). The evaluation provides the individual an opportunity to learn about the risks associated with transplantation, as well as the ongoing health maintenance required for successful transplantation outcomes (Dew et al., 2019).

Medication adherence among transplant recipients includes the components of initiation, implementation, and discontinuation, with each component viewed as a behavioral process (Vrijens et al., 2012). Solid organ transplantation requires an ongoing commitment to drug therapy and medical care, with transplant representing a unique chronic illness necessitating ongoing management, rather than a curative state (De Bleser et al., 2009). Heart transplant recipients require lifelong immunosuppression therapy to protect the transplanted organ from immunologic injury and graft failure (Dobbels et al., 2004; McCurry, 2019). Despite educational efforts during the transplant evaluation phase and following transplantation, medication nonadherence rates remain as high as 34.1% among heart transplant recipients, with nonadherence associated with a greater incidence of clinical events that include the development of transplant-related coronary artery disease and acute rejection events (Denhaerynck et al., 2018; Dobbels et al., 2004).

Medication adherence is multifactorial and represents an alignment between the individual's behavior and their prescribed medication dosing regimen (Gast & Mathes, 2019; Sabaté, 2003). Medication nonadherence among transplant recipients is associated with both intrinsic/patient-related factors, and extrinsic factors that can include contextual elements related to the healthcare system, healthcare policy, or other variables like social support (Denhaerynck et al., 2018; Sabaté, 2003; Stilley et al., 2010). Medication adherence represents a complex cognitive behavior in which individuals must develop a plan for adherence, adapt the plan as needed, encode the intention to take the medication, store this information, remember to take the medication at the correct time, and continuously assess whether doses were taken (Insel et al., 2006). Tasks such as adjusting to schedule changes, planning for the availability of medications, and remembering to pick up medications from the pharmacy require individuals to encode and store the intention to take the medication and to retrieve this information (Stilley et al., 2010). These memory processes represent the individual's cognitive ability to create, manage, and execute the medication-taking intention at the appropriate time in the future, and are an important component of medication adherence (Zogg et al., 2011).

Among heart transplant recipients, the data evaluating cognitive processing is mixed. There is some evidence suggesting improvement on cognitive measures when pre-transplant performance is compared to post-transplant performance; however few studies include age-matched comparison groups and there is a lack of research evaluating self-management and cognitive function in this group (Cupples & Stilley, 2005). There are several mechanisms through which heart transplant recipients can experience cerebral hypoxic injury that may impact cognitive processes, including acute global brain ischemia associated with cardiac arrest, prolonged (chronic) hypoperfusion associated with heart failure, and/or acute focal ischemia associated with stroke or microemboli. These mechanisms may have significant clinical implications related to the cognitive function of heart transplant recipients, with 40% of heart transplant recipients in one study displaying cognitive impairment defined as performance at least 1.5 standard deviations (SD) below normative means in one or more cognitive domains (Burker, Gullestad et al., 2017). Among long-term survivors of heart transplantation, 39% in one study displayed impaired test performance on cognitive measures, especially those that measured executive function, memory, processing speed, and language functions (Burker, Gullestad et al., 2017). Executive functions consist of cognitive control processes that assist with perception, decision-making, prioritization, sequencing, and overall self-regulation of behavior (Miyake & Friedman, 2012; Snyder et al., 2015). Additional research is needed to evaluate executive function/working memory ability and memory processes in heart transplant recipients, and to define the relationship between executive function and self-management abilities like medication adherence in this population.

Significance

Nonadherence to immunosuppression is associated with an increased risk for organ rejection, allograft vasculopathy, and death (De Geest et al., 2014). Immunosuppression nonadherence has been found to be a factor in up to 90% of late acute rejection events that occur after the first year following transplant, and in 13% to 26% of deaths among heart transplant recipients in single-center research studies (De Geest et al., 2005). A prospective cohort study found that for individuals who were nonadherent after their first year following transplant, the risk of a negative clinical event was doubled (Dobbels et al., 2004). In addition to the significant clinical outcomes, nonadherence to the therapeutic regimen is also associated with increased healthcare costs (De Geest et al., 2005). Despite the importance of adherence to immunosuppression medications following heart transplantation for the prevention of graft rejection and preservation of graft function, medication nonadherence rates following heart transplantation in the literature range from 20% to as high as 37% (De Bleser et al., 2009; Dobbels et al., 2017).

Causes for nonadherence because of decline in cognitive processes may occur directly through the failure to recall the intention to take the medication as intended, or indirectly through illness representations that can be shaped by the mental representation of the illness. Time since transplant, perceptions related to the necessity of medications, and the perceived impact of transplantation on life are factors that have been associated with higher rates of nonadherence in some solid organ transplant recipient populations (De Geest et al., 2014; Massey et al., 2015). Pre-transplant medication nonadherence has been found to predict post-transplant nonadherence (De Geest et al., 2014). Heart transplant recipients are at unique risk for cerebral hypoxic injury both before transplantation as a result of pathophysiologic processes that can occur during heart failure and treatment with mechanical circulatory support devices (MCSD), and following transplant as a result of cardiopulmonary bypass, heart structural remodeling, and inflammatory processes (Acampa et al., 2016; Cho et al., 2017). These mechanisms and their impact on executive function and working memory potentially influence the ability to adhere after transplantation. Additionally, evaluation of these variables has become increasingly important to assess in the context of aging (Insel et al., 2006), with the majority of individuals undergoing transplantation in their 50s, and the median survival extending beyond 11 years (McCurry, 2019; Stoehr et al., 2008). Evaluating the relationship between self-management behaviors like medication adherence and executive function will inform interventions designed to support adherence among individuals who have heart transplants.

Background

Cerebral Hypoxic Injury

Cerebral hypoxic injury can occur because of acute global hypoperfusion associated with cardiac arrest, because of acute local hypoperfusion due to stroke or microemboli associated with heart failure and mechanical circulatory support devices, or due to chronic prolonged hypoperfusion associated with a low output state from heart failure. While a sizable body of literature exists that describes the pathophysiologic impact of cerebral hypoxic injury as it relates to each of these mechanisms, an understanding of the impact of cerebral hypoxic events on the cognitive functioning and self-management ability of the heart transplant recipient is lacking. These mechanisms are important to consider, with one study finding that 24.3% of heart transplant recipients sampled had a history of cardiac arrest, and 21.6% had a history of cerebral bleeding or infarction (Burker, Gullestad et al., 2017).

The literature on sequela from cardiac arrest contributes significantly to the evidence on mechanisms associated with acute forms of cerebral hypoxia and their impact on cognitive function. Hypoxic-ischemic-neuronal injury is known to occur in cardiac arrest, causing initial cell injury, the production of reactive oxygen species, microglia activation, and the inflammatory cascade initiation leading to neuronal cell death (Chalkias & Xanthos, 2012; Perez et al., 2016). The hippocampus, in addition to the thalamus, amygdala, visual cortex, and frontal lobe, are thought to be especially vulnerable to hypoxic brain injury associated with cardiac arrest, as evidenced by neuropathological changes on imaging (Perez et al., 2016). The cerebral injury seen in cardiac arrest can lead to alterations in cognitive processing, specifically in alterations to spatial memory, long-term memory, and executive function, with these alterations potentially persisting following interventions like heart transplantation (Perez et al., 2016).

Patients awaiting heart transplantation may have periods of prolonged chronic global hypoperfusion associated with cardiogenic shock and low output states, thus hypoxia due to heart failure represents another mechanism that may impact cognitive processing and more specifically executive function. Research has shown that structural abnormalities including damage to the hypothalamus and anterior cingulate cortex, as well as cerebral infarcts and gray and white matter changes, are present in the heart failure population when compared to healthy controls (Havakuk et al., 2017; Ogren et al., 2014). These brain changes associated with heart failure are hypothesized as being a result of prolonged hypoperfusion associated with decreased cardiac output, resulting in decreased cerebral blood flow, hypoxia, and cerebrovascular dysautoregulation, impacting the brain’s mechanisms for altering vascular responses to blood pressure changes (Havakuk et al., 2017; Ogren et al., 2014). Increased inflammatory markers, including increased serum levels of interleukin 6 (IL-6), have been found in samples from persons with heart failure, highlighting a possible inflammatory mechanism that may also be associated with cerebral injury in this population, and may have implications for those that go on to receive transplantation (Havakuk et al., 2017).

Stroke can occur prior to or after heart transplantation, resulting in acute cerebral hypoxia and subsequent changes to cognitive processing and executive function. On autopsy, 72% of heart transplant recipients had neuropathological changes that included presence of cerebrovascular lesions, with these local infarcts thought be related to circulatory insufficiency from cardiogenic shock or arrhythmia, hypotensive episodes associated with severe hemodynamic changes, embolism associated with cardiovascular disease mechanisms such as valvular vegetations and use of mechanical support, or circulatory insufficiency and embolism as a result of acute or chronic changes to the cardiovascular endothelium in the setting of organ rejection (Ang et al., 1989). Reperfusion injury contributes to cerebral damage in addition to the lack of oxygen that occurs during acute injury (McCance, 2015; Pan et al., 2007). After return of blood flow, for example after cardiac arrest or in some cases after ischemic stroke, reperfusion injury occurs as a result of the generation of high reactive oxygen species, leukocyte infiltration, platelet and complement activation, post-ischemic hyperperfusion, and blood-brain barrier deterioration (McCance, 2015; Pan et al., 2007; Ritter et al., 2000). Cerebral reperfusion injury, in addition to alterations in gene expression and protein response, are posited as contributing to irreversible cerebral injury in cardiac arrest survivors (Buanes et al., 2015).

Mechanical Circulatory Support Devices

Care for individuals with heart failure has evolved to include the implantation of mechanical circulatory support devices such as left ventricular assist devices (LVADs), venoarterial extracorporeal membrane oxygenation support (ECMO), intra-aortic balloon pumps, percutaneously placed ventricular assist devices (Impellas), and total artificial hearts (Alkhouli et al., 2020; Cho et al., 2017; Hassett et al., 2020; Zalawadiya et al., 2017). While LVAD devices are commonly used as a bridge to transplantation, individuals who receive LVADs while awaiting transplant have only a 50% chance of obtaining a heart transplant within one year of receiving the mechanical circulatory support device, however their stroke risk is estimated to be around 9% per year (Merkler et al., 2019; Parikh et al., 2016). LVAD support is associated with a prothrombotic state, with ischemic stroke representing a major complication (Cho et al., 2017). While anticoagulation is used to prevent the generation of microemboli and larger clots (e.g., pump thrombus development) that can result in occlusive ischemic hypoxia, subsequent risk for intracranial hemorrhage also exists (Cho et al., 2019). In ECMO, cerebral infarcts can occur as a result of microemboli and thrombosis within the ECMO cannula and as a result of impaired cerebral autoregulation associated with shifts from severe hypercapnia during respiratory failure to a normocapnic state (Xie et al., 2017). ECMO is also associated with brain injury due to increased risk for intracranial hemorrhage which may occur due to systemic inflammatory responses that cause disruption to the blood-brain barrier and neuronal damage, generation of thrombin and inability to balance a procoagulant and anticoagulant state, and the functional changes in pressure associated with the ECMO circuit itself which may cause lysis of blood cells and platelets (Xie et al., 2017).

Memory Processes

Mild cognitive impairment (MCI) may impact a large proportion of heart transplant recipients, with one study finding that 30.1% of long-term survivors of heart transplant qualified for MCI based on cognitive measures, with especially poor performance on memory, processing, language, and executive function evaluations (Burker, Gude et al., 2017; Burker, Gullestad et al., 2017). Mild cognitive impairment (MCI) represents an interval between ideal cognitive functioning and clinical dementia, however the cognitive declines associated with MCI do not necessarily indicate ultimate progression to dementia or Alzheimer’s disease (Petersen et al., 2014). Lack of screening for MCI prevents diagnosis and ultimately the ability to evaluate for reversible causes and to support the patient in developing self-management strategies should cognitive function continue to decline (Sanford, 2017). Changes in memory and cognitive processes can impact the individual’s ability to learn and recall information (Sanford, 2017). This is especially concerning for heart transplant recipients, who must employ and modify self-management strategies frequently throughout their clinical course, and who are living longer due to advancements in transplant surgery and medical management (OPTN, 2020). Cerebral hypoxic injury may represent a major risk factor for MCI, in addition to the variety of other reversible and irreversible causes of MCI in the heart transplant recipient, warranting further consideration into the prevalence of memory process alterations in this population and their relationship to medication adherence.

Executive Function/Working Memory

Executive functions are the higher-level cognitive skills including working memory, inhibition, and shifting that are used in the organization and regulation of behavior, are particularly important to consider when evaluating self-management, and may be impacted by cerebral injury (Miyake & Friedman, 2012; University of California San Francisco, n.d.). These processes are defined in Table 1. Working memory refers to the specific system underlying the use and maintenance of limited information during the performance of a cognitive task, incorporating both the storage and manipulation of information (Baddeley, 2012; Miyake & Shah, 1999). Executive function includes cognitive processes that regulate individual thoughts and behaviors, with previous research providing evidence to support that a relationship exists between executive function and medication adherence across a wide range of chronic disease states and populations (Alosco et al., 2012; Ettenhofer et al., 2010; Hinkin et al., 2002; Insel et al., 2006; Mayo et al., 2016; Stilley et al., 2010).

Table 1

Executive Function Processes

Executive Function Process	Definition
Shifting	Switching between tasks.
Inhibition	Resisting an automatic response in order to make a more task-relevant response.
Updating	Monitoring and coding incoming information. Replacing outdated information with the newer more relevant information.
Working Memory	Maintaining, manipulating, and using limited information during the performance of a cognitive task across a short delay.

Note: Adapted from Snyder, H., Miyake, A., & Hankin, B. (2015). Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. *Frontiers in Psychology*, *6*, 328. https://doi.org/10.3389/fpsyg.2015.00328. Copyright 2015 by Frontiers Media SA.

Theoretical Framework

Leventhal's common-sense model (CSM) of self-regulation was selected as the theoretical foundation for this research. The CSM is particularly useful for understanding the processes that are involved in the initiation, maintenance, and transition of adherence behaviors through the systematic development of representations that influence procedures for self-management (Leventhal et al., 2016). Stimuli act upon the individual's memory structures, producing mental models that act as representations of illness threats, comprised of the domains of identity, cause, consequence, control, and timeline, which ultimately influence action plan development and behavior (Leventhal et al., 2003; Leventhal et al., 2016).

Illness Representations

Understanding illness representations may be especially applicable for understanding adherence among individuals who transition from a state of end-stage organ failure to life as a transplant recipient. Transplantation care requires extensive ongoing follow up but may not consist of the same concrete experiences of general symptoms, ultimately affecting how symptoms and labels impact the individual's personal representation. Among individuals with asymptomatic chronic conditions like many of those who have received an organ transplant, there may be a discrepancy between the individual's representation and the actual physiological demands of the disease process, contributing to medication nonadherence (Leventhal et al., 2016). Illness coherence is the extent to which an individual's representation contributes to a coherent understanding of their condition or illness (Moss-Morris et al., 2002), and may be especially important to consider in this population. Among kidney transplant recipients, perceived necessity of medications and perceived impact of transplantation on the individual's overall life have been shown to decrease over time (Massey et al., 2015). There is also evidence to suggest that perceived susceptibility to rejection and length of time since transplantation are major predictors of adherence to immunosuppression following kidney transplant (Kung et al., 2017). Illness perceptions have been clearly defined as a variable in the kidney transplant population, and when heart transplant recipients are grouped with other solid organ transplant recipients, there is evidence to suggest that perceptions surrounding transplantation and medications are associated with adherence (Kung et al., 2012). These perceptions allude to the larger mental models that encompass the incorporation of the awareness of health threats, the formulation/organization of behaviors, and subsequent action plan development, operating within a feedback system that continuously evaluates action plan efficacy and progression (Leventhal et al., 2003; Leventhal et al., 2016).

While much of the research on illness representations has focused on kidney transplant recipients or samples of mixed solid organ recipients, there may be differences in perception among heart transplant recipients, particularly when considering the impact that cerebral hypoxic injury and potential executive function and memory process alterations may have on representation development. The clinical course for heart transplant recipients is unique and includes an increased cumulative risk for cerebral injury, with one study identifying cognitive impairment in 40% of the heart transplant recipients sampled, with cerebrovascular pathology identified in over 30% of those studied (Burker, Gullestad et al., 2017). These differences, in additional to overall variances in post-transplant care, necessitate the need for an examination into the self-management behaviors of heart transplant recipients separately from other groups. Incorporating concepts from Leventhal's CSM, in addition to cognitive control processes and the associated pathophysiologic processes that may contribute to these, will provide a model that can assist with research that seeks to examine the self-management of medications among this population.

Cognitive Control Processes

Cognitive control processes consist of the allocation of mental resources used during goal-directed behavior, and are ultimately responsible for controlling what information and stimuli reach awareness (Mackie et al., 2013). While often used interchangeably with the term executive control, these processes are functionally associated with the anterior cingulate cortex and frontal lobe and are comprised of diverse but interrelated components including task shifting, updating and monitoring working memory representations, and inhibition (Mackie et al., 2013; Miyake et al., 2000). Updating represents an executive function that requires active monitoring and manipulation of information into working memory and may be especially important during repetitive behaviors like medication taking, particularly when shifting between tasks is required (Insel et al., 2006; Miyake et al., 2000). Individuals must hold and process information related to medication taking, ultimately updating working memory representations via the incorporation of new, more relevant information (Insel et al., 2006; Miyake et al., 2000). These cognitive processes are important to consider in the context of the cognitively-derived illness representations that ultimately guide coping procedures, action plan development, and individual appraisals of behavior.

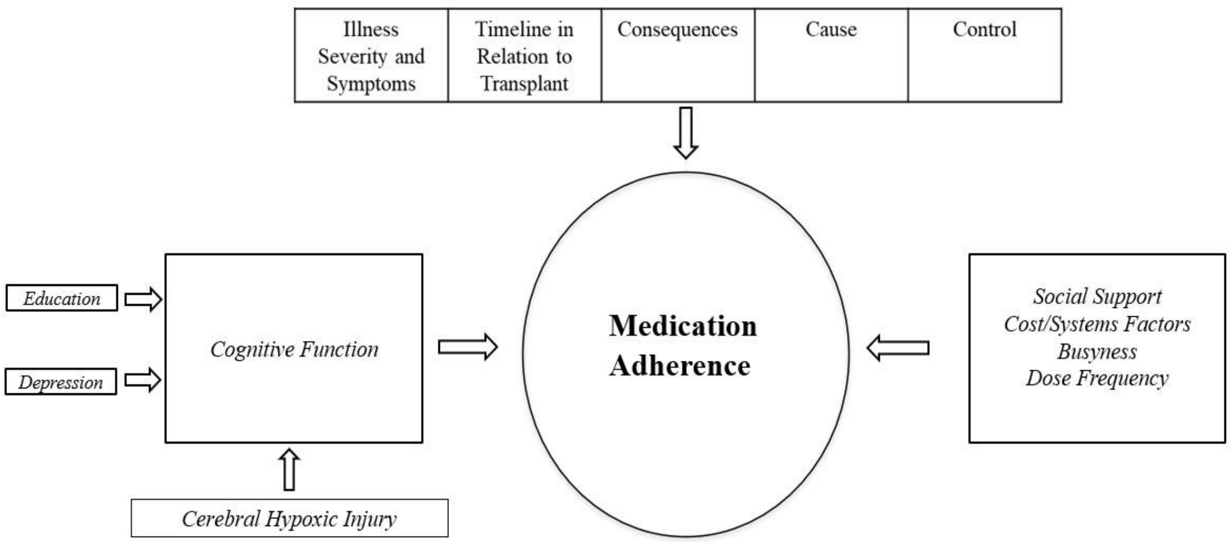
Adapting Leventhal's CSM

The manuscript entitled *A Conceptual Model on Medication Adherence Among Heart Transplant Recipients* (Appendix A) describes the process that was used to adapt Leventhal's CSM into the conceptual model that guided this research.

Figure 1 adapts components of Leventhal's CSM into a model that illustrates the proposed role of illness representations and cerebral hypoxic injury mechanisms in influencing medication adherence in the heart transplant recipient. This model demonstrates the complexity of self-management behaviors in this population and seeks to elucidate the variables that may impact the ability of heart transplant recipients to adhere to their medications.

Figure 1

Conceptual Model of the Mechanisms Contributing to Cognitive Function Alterations and Medication Adherence in Heart Transplant Recipients



Note. Adapted from Insel (n.d.) Cognitive Enhancement Model for Medication Adherence (CEMMA) and Leventhal et al. (2003) Common Sense Model of Illness Self-Regulation.

Overview and Purpose

The purpose of this study was to describe the relationships between cognitive function (executive function & memory), illness perceptions, and medication adherence among heart transplant recipients with the goal of expanding insights into factors associated with non-adherence to immunosuppression following heart transplantation. This knowledge has the potential to inform the development of interventions to improve adherence and clinical outcomes.

Specific Aims

Aim 1

Examine associations between executive function/working memory, cognitive impairment, illness perceptions, demographic variables, and medication adherence in heart transplant recipients.

Aim 2

Examine associations between executive function/working memory, cognitive impairment, demographic variables, medication adherence, and history of use of mechanical circulatory support devices, cardiac arrest, and/or stroke.

Aim 3

Predict medication adherence using executive function/working memory, cognitive impairment, and history of use of mechanical circulatory support devices.

Summary

Medication adherence among heart transplant recipients is a complex area of self-management. Nonadherence prevalence in an international study was as high as 34.1%, and a variety of multilevel factors were associated with adherence including patient intention and perceived barriers (Denhaerynck et al., 2018). The poor clinical outcomes associated with nonadherence in heart transplant recipients warrants further examination into the patient-level factors that may be implicated. Developing an understanding of the role of cerebral hypoxic injury, executive function, cognitive impairment, and illness perceptions is necessary to advance the science of self-management in this group. Applying concepts from Leventhal’s CSM into a model of the mechanisms contributing to cognitive function alterations and medication adherence in heart transplant recipients offers a new theoretical viewpoint for the study of self-management in this population.

Literature Review

The cognitive processes used in the organization and regulation of behavior, also known as executive functions, are particularly important to consider as it relates to self-management behaviors like medication adherence (Dajani & Uddin, 2015; Miyake & Friedman, 2012; University of California San Francisco, n.d.). This section will provide additional information on the injury mechanisms that may impact executive function and memory processes among heart transplant recipients given their increased cumulative risk for cerebral injury (Burker, Gullestad et al., 2017). The role of executive function and memory processes in medication adherence behaviors within solid organ transplantation and in other chronic disease states will be described, highlighting the gap that exists in the current literature and providing a foundation for the development of the research study.

Overview of Medication Adherence Following Heart Transplantation

The risks associated with medication nonadherence following transplantation have led to the prioritization of research that analyzes psychosocial factors. Pretransplant medication nonadherence has been found to predict posttransplant nonadherence among transplant recipients, with nonadherence increasing over time (De Geest et al., 2014). Depression has also been found to be a predictor of poor adherence among heart transplant recipients specifically, with feelings of guilt and indebtedness to the donor possibly contributing (Delibasic et al., 2017; Shemesh et al., 2017). Other psychosocial variables have shown only weak correlations to medication adherence in previous research (Dew et al., 2007).

More recent research has focused on considering the impact of systems-level variables on adherence. Patient level barriers to taking medications, including challenges reading and comprehending health-related materials, and cost-related challenges associated with affording medications, were each found to be independently associated with nonadherence (Denhaerynck et al., 2018). New attention has turned to developing adherence promoting interventions, with multicomponent interventions proving efficacious in some studies that target adherence in the general solid organ transplantation populations; however, the specific components that are responsible for these improvements are not clearly defined or understood (Dew et al., 2017; Dobbels et al., 2017). Among kidney transplant recipients specifically, adherence interventions that focused on the establishment of daily routines and environmental cues have been successful in improving medication adherence (Russell et al., 2020). While these interventions show promise, variations in life expectancy, morbidity risks, and adherence barriers may differ by organ type, challenging the implementation of general adherence-promoting interventions that may not address the needs of recipients of specific organs (Dew et al., 2017). In fact, among heart transplant recipients specifically, there is weak evidence that psycho-educational interventions have an impact on adherence (Marcelino et al., 2015).

This research highlights the gap that exists in understanding the medication adherence behaviors of heart transplant recipients and limits the development of adherence-promoting interventions for this group. Heart transplant recipients may have unique differences when compared to other solid organ recipients, particularly as it relates to their risk for cerebral injury and incidence of cognitive impairment (Burker, Gullestad et al., 2017). Complex cognitive tasks are involved in post-transplant self-management behaviors including medication adherence, necessitating a greater understanding of the cognitive outcomes of individuals that experience cerebral injury prior to heart transplantation (Cupples & Stilley, 2005). Understanding the pathophysiological and functional outcomes associated with cerebral hypoxic injury may provide new insight into the self-management of this population.

Cognitive Outcomes Associated with Cerebral Hypoxic Injury

Animal Models

Animal studies provide a foundational understanding of the complex physiological changes that occur in acute and chronic cerebral hypoxic processes. Animal models of cerebral hypoxic injury are designed to mimic injury in humans, providing mechanisms through which cognitive processes may become altered, and providing evidence as to the behavioral changes that can occur following cerebral hypoxic episodes that simulate injury in humans.

Monkey and pig models of acute cerebral hypoxia during cardiac arrest demonstrate disruption of cell membrane ion pumps and altered homeostasis following the depletion of ATP (adenosine triphosphate) stores, with calcium efflux pump failure and release of glutamate and other amino acids, which activate the *N*-methyl-D-aspartate (NMDA) receptors, further increasing calcium within the intracellular space (Reis et al., 2017). Subsequent extracellular flooding with enzymes such as proteases and lipases occur, causing cell injury and destruction (Perez et al., 2016). Mitochondrial overload, oxidative damage, and loss of ATP production followed by cell death takes place (Reis et al., 2017). Additional cerebral injury can occur following resuscitation and return of cerebral blood flow via microglia activation, infiltrative macrophages, and the release of pro-inflammatory cytokines that perpetuate injury (Reis et al., 2017).

Areas of the brain with high amounts of glutaminergic neurons and those with high metabolic rates and oxygen demands are thought to be more vulnerable to cerebral hypoxia (Perez et al., 2016). The four-vessel occlusion method is one technique that can induce transient forebrain ischemic injury in animals, resulting in irreversible damage to neurons including CA-1 pyramidal cells in the hippocampus (Volpe et al., 1984). With this model, there is neuropathological evidence of neuron loss and proliferation of gemistocytic astrocytes leading to reactive astrogliosis and scar formation (Sofroniew & Vinters, 2010; Volpe et al., 1984). The hippocampus is embedded in the cerebral cortex and is associated with memory and cognitive flexibility and exists as part of a neurological network that regulates emotions and allows for representation development (Rubin et al., 2014). Hippocampal injury is associated with deficits in learning and memory impairment in animal models, with "working memory" tasks such as delayed alternation in T- or Y-maze performance, spatial learning abilities in radial and water maze tests, and alterations in conditional responses reported (Nunn & Hodges, 1994). Animals with four-vessel occlusion had altered performance on "working" and "reference" tasks during maze performance, with these deficits comparable to cognitive deficits seen in humans following cerebral hypoxic injury (Volpe et al., 1984).

In animal models of stroke, cerebral injury is characterized by a reduction in cerebral blood flow, which causes a cascade that includes inhibited protein synthesis, ATP store depletion, and membrane depolarization which results in the opening of calcium channels and disruption in neuronal homeostasis (Grotta & Helgason, 1999). Extracellular potassium is released, lactic acidosis occurs, and glutamate is released, which activates the *N*-methyl-D-aspartate (NMDA) receptors, causing subsequent increased sodium permeability which results in edema (Grotta & Helgason, 1999). Intracellular calcium continues to rise in the setting of activated NMDA ion channels, which activates additional destructive enzymatic pathways (Grotta & Helgason, 1999). Cellular membrane integrity and mitochondrial function are damaged by enzymatic activity and free radical production that occurs as a result of enzyme activity (Grotta & Helgason, 1999). Inflammatory cascades, including the release of cytokines, increase tissue inflammation and may have a role in further damaging vascular endothelium in the brain as a result of white blood cell activity (Grotta & Helgason, 1999). In another animal model in which rats had induced prefrontal cortex ischemia as a result of endothelin-1 injections into the medial prefrontal cortex, executive function was impaired as evidenced by selective attention and set shift impairment (Cordova et al., 2014). These models provide insight into the mechanisms of cerebral hypoxia that may occur during cerebral hypoxic events in humans and provide a foundational understanding of the effects of hypoxic injury on cognitive processes.

Functional Outcomes in Humans

Functional outcomes, in particular executive function alterations, are of particular concern in heart transplant recipients that have experienced cerebral hypoxic injury during their disease process. There is mixed data regarding the presence of cognitive dysfunction following heart transplant related to inconsistencies in measurement and differences in the timing of assessments, with a paucity of research into executive function alterations specifically (Cupples & Stilley, 2005). Despite inconsistencies in measurement, there is research that suggests that a portion of cardiothoracic transplant recipients experience some level of cognitive alterations when compared to normative and age-matched controls (Cupples & Stilley, 2005; Schall et al., 1989). Schall et al. (1989) compared pre- and post-heart transplant cognitive assessment scores in a sample of heart transplant patients, with results indicating no significant improvement in cognitive function scores despite improved overall physical health. There is additional evidence to suggest that while motor speed has been shown to increase following heart transplantation, deficits in cognitive functioning including attention, concentration, verbal learning, and abstract reasoning persist (Nussbaum & Goldstein, 1992). There is a great need to further evaluate the changes that occur as a result of cerebral hypoxic injury in this population, with special focus on executive function and memory processes as it relates to ongoing self-management behaviors following transplantation (Burker, Gude et al., 2017). Research into the specific mechanisms of cerebral hypoxic injury may provide insight into the pathways that may impact the heart transplant recipient's executive function and memory processes.

Research suggests that hypoxic-ischemic injury, reperfusion injury, neurodegeneration changes, and tissue atrophy have deleterious effects on attention, long-term memory, spatial memory, and executive function even in remote survivors of cardiac arrest (Chalkias & Xanthos, 2012; Perez et al., 2016). Buanes et al. (2015) found that around twenty-nine percent of cardiac arrest survivors in one sample experienced cognitive impairment four years after the arrest event, evidenced by impaired executive function and short-term memory, with medial temporal lobe and hippocampal damage postulated to be the cause of these deficits. Individuals who survive sudden cardiac death may have cognitive dysfunction as a result of ischemic or hypoxic brain injury sustained during the arrest, and while the cognitive impairment sustained from cardiac arrest may improve within the first three months following the event, a substantial number of patients remain impaired after one year, particularly in the executive functioning domain (Steinbusch et al., 2017).

In heart failure patients who do not experience cardiac arrest, alterations to verbal learning and memory have been identified, possibly related to the compounding effects of comorbidities and chronic, prolonged global hypoperfusion, with structural brain abnormalities identified on magnetic resonance imaging (MRI) (Hawkins et al., 2012; Ogren et al., 2014). Individuals who receive heart transplantation often have end-stage heart failure, however even upon obtainment of improved cerebral blood flow following transplantation, one study found that a third of the recipients sampled had ongoing evidence of cerebrovascular pathology on MRI (Burker, Gullestad et al., 2017; Gruhn et al., 2001).

Stroke-induced cognitive deficits may vary however information processing and executive function deficits are common in individuals following stroke, even when more pronounced effects are absent (Cumming et al., 2013). In individuals who required mechanical circulatory support prior to transplantation, silent cerebral infarctions as a result of microemboli may have induced executive cognitive dysfunction and frontal lobe damage in the absence of clinically diagnosed stroke, further illustrating the potential deleterious prothrombotic state associated with these devices (Komoda et al., 2005). In another study, lower cognitive function scores on neuropsychological testing were seen in heart transplant recipients that received a ventricular assist device prior to transplantation when compared to individuals that did not have a pre-transplant ventricular assist device (Dew et al., 2001). Heart transplant recipients are also at increased risk for stroke following transplantation, with operative complications, local and systemic inflammation, and electrical and structural remodeling of the myocardium and associated incidence of atrial fibrillation potentially implicated (Acampa et al., 2016).

Cerebral microbleeds in small cerebral vasculature related to conditions like hypertension may be associated with impaired executive function and cognitive impairment in patients with stroke (Sun et al., 2014). Neuroanatomical lesions in the hippocampus and white matter are thought to specifically contribute to the pathogenesis of cognitive impairment following stroke (Sun et al., 2014). Inflammation, white matter changes, and tissue atrophy may also contribute to alterations in cognitive processes in stroke survivors (Kulesh et al., 2018). Kulesh et al. (2018) sought to examine the role of inflammation in cognitive impairment following acute ischemic stroke by evaluating serum concentrations of IL-6, tumor necrosis factor-alpha, and interleukin 10 (IL-10). All stroke survivors had higher levels of IL-10 present in serum compared to the control group of healthy individuals, however the patients that had dysexecutive cognitive impairment had higher concentrations of IL-6 present in serum, and lower fractional anisotrophy of the thalamus on MRI than the stroke survivors without cognitive impairment, highlighting the role that inflammation likely has in post-stroke cognitive impairment (Kulesh et al., 2018).

Implications for Heart Transplant Recipients

There are several mechanisms, including cerebral injury via acute global brain ischemia associated with cardiac arrest, via prolonged (chronic) hypoperfusion associated with heart failure, or via acute focal ischemia associated with stroke, which may impact the functional outcomes of heart transplant recipients. A deeper understanding of the role of executive function/working memory and memory processes, particularly in the context of cardiac arrest, stroke and mechanical circulatory support, is needed to better understand and support the self-management abilities of heart transplant recipients.

Medication Adherence and Executive Function

In Transplantation

A literature search found that most of the studies that include cognition as a variable among heart transplant recipients were focused on cognition as a component of behavioral interventions or mobile technology affinity rather than on assessments of cognition as it relates to medication adherence (Berben et al., 2011; De Bleser et al., 2009; Reber et al., 2018; Senft et al., 2017). Two of these studies were descriptive, with aims that included the evaluation of practice patterns to improve adherence among transplant centers and medication adherence among older adults with heart failure.(Howell et al., 2017; Senft et al., 2017). One of the studies focused on the neuropsychological profile of heart transplant candidates, using a battery of 13 tests across several cognitive domains, with a cross-sectional analysis finding that executive functions were often impaired among individuals with end-stage heart disease (Mapelli et al., 2011). Medication adherence was not measured, nor was further data collected following heart transplantation (Mapelli et al., 2011). The initial search highlighted a gap in considering how cognitive processes such as executive function may impact medication adherence among heart transplant recipients, as none of the studies measured both phenomena in this population.

In kidney transplantation, the findings on cognition and adherence are mixed. One study found that neurocognitive ability may have an indirect role in medication adherence via self-efficacy and depression (Paterson et al., 2018), with everyday problem solving measures found to be predictive of adherence when traditional neuropsychological tests were not (Gelb et al., 2010). In considering medication knowledge, there is evidence that kidney transplant recipients with mild cognitive impairment score significantly lower on measures of treatment knowledge when classified using the Mini-Mental State Examination (MMSE) (Patzer et al., 2016). Elderly kidney transplant recipients in particular have high rates of forgetting medications (30%) even in samples that exclude those with cognitive limitations, suggesting that actual rates of nonadherence may be much higher and indicating a need to generate research that examines both cognition and medication adherence in this population (Tielen et al., 2011). In liver transplantation, an association between cognition and medication adherence has not been elucidated, with no evidence of a relationship between cognition and self-management behaviors (Ko et al., 2019), or medication adherence (Serper et al., 2015).

One consistent finding in the literature examining medication adherence in transplant recipients is the screening out of individuals based on cognitive measures, often via the MMSE. The MMSE is a less sensitive measure of cognitive impairment compared to other measures like the Montreal Cognitive Assessment, indicating that the prevalence of mild cognitive impairment in this population may be higher than previously reported (Patzer et al., 2016). By excluding individuals who perform poorly on the MMSE from research that seeks to examine medication adherence among transplant recipients, a clear picture of the association between cognitive function and medication adherence cannot be attained.

Other Chronic Disease States

The manuscript titled *Executive Function and Medication Adherence in Adults: A Scoping Review* (Appendix B) provides an overview of the evidence supporting a relationship between executive function and medication adherence across a diverse range of chronic disease states.

Summary

Research indicates that long-term survivors of heart transplantation may have cognitive alterations and that heart transplant recipients have a high cumulative risk of cerebrovascular pathology over their lifetimes, with several pathophysiologic processes potentially contributing (Burker, Gullestad et al., 2017). There is strong evidence that executive function can predict adherence in certain populations (Insel et al., 2006) but there is a paucity of research examining how cognitive processes may be involved in self-management skills like medication adherence among heart transplant recipients. Furthermore, previous research has often failed to utilize measures that are sensitive enough to detect subtle deficits in cognitive processing, frequently relying on the MMSE rather than on other measures that include executive function components (Cupples & Stilley, 2005). Interventions that have included consideration for cognitive processes in their design have been effective in improving adherence when compared to simple educational initiatives or reminders in other populations (Insel et al., 2016). Together these findings suggest there is a strong need for further analysis into the role that cognitive processes have on medication adherence among heart transplant recipients.

CHAPTER II: PRESENT STUDY

The purpose of this study is to examine executive function/working memory, cognitive impairment, illness perceptions, and medication adherence among heart transplant recipients. This chapter will discuss the methods that were used in the study, including study design, sampling, instrumentation, procedures, data management, data analysis, human subject protections, results, and discussion. Additionally, the manuscript titled *Immunosuppression Medication Adherence Among Heart Transplant Recipients: Relationships with Cognitive Function, Depression, and Illness Perceptions* (Appendix C) provides details on the study design and results and will be referenced in this chapter.

Study Design and Overview

The lack of research examining executive function, cognitive impairment, illness perceptions and self-management behaviors among heart transplant recipients warranted the use of a descriptive, cross-sectional design to examine associations between the variables of interest. Observational studies are appropriate when the size and direction of relationships amongst variables needs to be further elucidated, making this design choice appropriate to address the research aims (Shadish, 2002).

Setting

This study took place at the Mayo Clinic Transplant Center, which is home to a medium-sized heart transplantation program and manages the care of over 400 heart transplant recipients. Approval to conduct this research was received from the University of Arizona Human Subjects Protection Program (2106868392) and from the Mayo Clinic Institutional Review Board (21-001508), with Mayo Clinic serving as the institution of record (Appendix D).

Sample

A convenience sample of adult heart transplant recipients (e.g., age > 18 years), women and men, were recruited from the Mayo Clinic Transplant Center.

Inclusion and Exclusion Criteria

Heart transplant recipients that were over six months past their transplantation surgery were recruited. This criteria was based off of the transplant center's requirement that individuals have a caregiver for the first three months following transplantation to assist with self-management behaviors like medication adherence, and the transplant center's medication weaning protocol wherein individuals are retained on higher doses of corticosteroids that may impact cognitive processes for the first few months following transplantation. Participants were required to be able to read, write, and understand English given the format of the measures that were used.

Individuals with a confirmed diagnosis of dementia were excluded. Additional exclusion criteria included active substance abuse given its potential impact on cognitive function. Individuals who were not independently managing their own medications (e.g., those that are reliant on a caregiver or facility) were also be excluded. Women who were pregnant or attempting to become pregnant were excluded. Participants who were admitted to the hospital during data collection were excluded, given that the hospitalization may have interfered with their ability to recall medication adherence prior to their admission.

Sample Size

Using G*Power 3 software, a sample size of at least 34 was targeted based on previous research indicating that this sample size allows for the detection of small differences in cognitive function of one standard deviation, with required power of 0.8 and level of significance of .05 (Burker, Gullestad et al., 2017).

Sampling and Recruitment

Recruitment strategies for the convenience sample were initially intended to include physician/transplant team referrals, portal-message requests, and informational sessions at the beginning of weekly support group meetings. However, once recruitment began, the volume of responses to portal message inquiries negated the need to use other strategies. Recruitment via patient portal was done on a rolling basis until the desired sample size was achieved. After individuals expressed interest via the portal, the researcher called them to discuss the study, obtain electronic informed consent for the study procedures, and scheduled the telephone study session.

Measures

Demographic and Medical Variables

Demographic data were obtained from the participants, including age, gender, race/ethnic background, and highest obtained education. Education was incorporated due to the conflicting evidence as to the role of education in post-transplantation outcomes and adherence (Allen et al., 2012; Dobbels et al., 2009).

Questions on medical variables of potential importance, including history of stroke, cardiac arrest, and/or mechanical circulatory support device implantation, were also asked during the demographic questionnaire. These variables were selected because of previous work that found that almost a quarter of heart transplant recipients in one study had a history of cardiac arrest and over 20% had a history of cerebral bleeding or infarction (Burker, Gullestad et al., 2017). Poorer cognitive status has been identified after transplantation among individuals that received left ventricular assist devices, necessitating the inclusion of this variable for the purposes of evaluating the use of mechanical circulatory support devices and their associations with the other variables of interest (Dew et al., 2001). Historical information on these medical variables was also obtained from within the electronic health record, given that patients may not be able to recount whether they experienced these medical events or received these devices during their transplantation care. The obtained information included data on type and duration of mechanical circulatory support, not including cardiopulmonary bypass time during the transplantation surgery.

Basel Assessment of Adherence to Immunosuppressive Medications (BAASIS©)

The Basel Assessment of Adherence to Immunosuppressive Medications (BAASIS©) was used as a self-report assessment of medication adherence. The BAASIS© measure includes the dimensions of immunosuppression medication taking and timing, making it appropriate for use in transplant populations given the importance of regularity of medication intake (Dobbels et al., 2010). This measure also includes a recall period of four weeks and can be performed in interview format or via administered questionnaire (Dobbels et al., 2010). Permission to use this measure was obtained from the University of Basel, Leuven-Basel Research Group.

Validity and Reliability

Predictive validity concerns the correlation of a future criterion with the selected measure, and items on this measure have been shown to have good predictive validity when used in HIV positive individuals to predict virological failure (Carmines & Zeller, 1979; Dobbels et al., 2010). Concurrent validity can be assessed by correlating the measure and the criterion at the same point in time, and the BAASIS© has also demonstrated good concurrent validity when compared to electronic monitoring (Carmines & Zeller, 1979; Dobbels et al., 2010). A transculturally adapted version of this measure produced a Cronbach's alpha of 0.7, indicating acceptable internal consistency, and factor analysis was used to evaluate construct validity, with results supporting the dimensional structure of the measure (Marsicano Ede et al., 2013).

Interpretation of Score

The BAASIS© consists of questions that are answered as either "yes" or "no," and for answers of "yes," individuals are asked to indicate how often the event has happened in the past one month (Dobbels et al., 2010). Questions include data on missing doses, drug holidays, time deviations greater than two hours, dose changes or discontinuation without a provider's consultation (Gustavsen et al., 2019). This measure is easy to score, with any deviations in any of the items considered nonadherence (Dobbels et al., 2010).

Laboratory Immunosuppression Trough Data

Laboratory trough data (e.g., plasma concentrations of immunosuppression medications) was obtained via the electronic health record. Several medications, including tacrolimus/Prograf, sirolimus/Rapamune, everolimus/Zortress, and cyclosporine require ongoing monitoring as part of the transplant recipient's care. Due to several variables known to impact trough data, such as other medications, overall renal function, and provider dose changes, these data were used as a secondary measure of adherence. The trough data from the participant's previous six lab draws were included in the analysis. Previous research indicates that combining adherence measures may identify different transplant recipients as nonadherent, thus this study utilized laboratory trough variability and self-report to measure this variable (Gustavsen et al., 2019).

Brief Illness Perceptions Questionnaire (Brief IPQ)

The Brief Illness Perceptions Questionnaire (Brief IPQ) is designed to evaluate the illness representation dimensions, or the cognitive and emotional models that characterize individual interpretations of illness identity, consequences, timeline, control/cure and cause within a short timeframe (Broadbent et al., 2006). The concept of illness representations is derived from Leventhal's CSM, with the appraisal process, representation formation, and coping procedures interacting in a feedback loop (Broadbent et al., 2006). The Brief IPQ has been adapted and applied to transplantation recipients in order to measure how individuals perceive their transplant, incorporating concerns about rejection and the emotional response to transplant in the place of the more general "illness" term (Broadbent et al., 2006; Massey et al., 2015). The adapted version utilized by Kung et al. (2012) was used for this study, and approval to use this measure was obtained from Dr. Elizabeth Broadbent.

Validity and Reliability

The Brief IPQ has shown evidence of good predictive validity when used to assess patients recovering from myocardial infarction, and discriminant validity has been supported based on the measure's ability to distinguish between different illness/disease processes (Broadbent et al., 2006). The Brief IPQ has also shown good evidence of concurrent validity when compared to the longer Revised Illness Perceptions Questionnaire (Broadbent et al., 2006). The Brief IPQ has demonstrated good test-retest reliability among renal disease patients, however internal consistency cannot be measured given that each item reflects a singular dimension (Broadbent et al., 2006; Broadbent et al., 2015).

Interpretation of Score

The Brief IPQ uses a scale from 0 to 10 with higher scores indicating stronger perceptions on that particular dimension, except the causal dimension which allows for an open-ended response (Broadbent et al., 2015).

Brief Test of Adult Cognition by Telephone (BTACT)

The Brief Test of Adult Cognition by Telephone (BTACT) is an assessment of cognitive functioning that is designed to be conducted via the telephone, and incorporates multiple dimensions including episodic memory, working memory, reasoning, verbal fluency, and executive function (Lachman et al., 2014). Originally designed to support evaluations of cognitive aging, the BTACT has been used to screen and track executive and memory function among post-transplant liver recipients (Ferman et al., 2019; Lachman et al., 2014). The BTACT can also be used to provide a composite measure of cognitive function, and has been applied to diverse populations (Tun & Lachman, 2006). Approval to use the BTACT was received from Dr. Lachman.

Validity and Reliability

The BTACT has demonstrated convergent validity via correlations with in-person Boston Cognitive Battery factors (short-term memory, verbal ability, reasoning, speed), with correlations ranging from .42 to .54, and all results reaching significance (Lachman et al., 2014). Evidence of good test-retest reliability has been demonstrated in two reliability studies via alternate forms reliability coefficients that were all significant at different times of measurement (Lachman et al., 2014). In one study, alternate form reliability coefficients ranged from .54 to .84 except for category fluency, and in the second study they ranged from .54 to .84 (Lachman et al., 2014).

The BTACT has also demonstrated reliability via test-retest correlation coefficients that were significant in both studies (Lachman et al., 2014).

Interpretation of Score

Scoring procedures are available through Brandeis University, with an emphasis on accuracy of responses (Lachman et al., 2014). The *Midlife in the United States* longitudinal study, which incorporated 4,268 participants and included demographic variables including age, education, and gender, can be used to provide normative data for comparison when using the BTACT (Lachman et al., 2014).

Telephone Montreal Cognitive Assessment (t-MoCA©)

A telephone version of the Montreal Cognitive Assessment (t-MoCA©) that does not require visual stimulus or written responses has been used as a test of cognition after transient ischemic attacks (TIAs) and stroke to detect cognitive impairment among community-dwelling older adults (Pendlebury et al., 2013). The Montreal Cognitive Assessment (t-MoCA©) is widely recognized as an effective measure to assess for milder forms of cognitive impairment, and the telephone-adapted version allows for the administration of this measure except for the visuoexecutive and naming components (Castanho et al., 2014). Permission to use this measure was obtained from the MoCA Clinic and Institute.

Validity and Reliability

Freitas et al. (2012) used confirmatory factor analysis to corroborate the six-dimension structure of the in-person MoCA and provided evidence to support construct-related validity (Freitas et al., 2012). The MoCA has also demonstrated evidence of discriminant validity using the Rasch model (Freitas et al., 2014; Freitas et al., 2012). Nasreddine et al. (2005) found that the

MoCA demonstrated good test-retest reliability, indicating consistency across time, and the internal consistency is also good, yielding a Cronbach alpha on the standardized items of 0.83. Test-retest reliability in detecting MCI among individuals with stroke or TIA for the telephone version of the MoCA was 0.75, indicating moderate/good reliability (Pendlebury et al., 2013).

Interpretation of Score

The original MoCA possesses testing components that are associated with a designated number of points, with scores of 25 or below indicating impairment, and scores adjusted for education with ‘1’ point added for individuals with 12 years of education or less (Nasreddine et al., 2005). Pendlebury et al. (2013) found that optimal sensitivities and specificities for detection of MCI on the t-MoCA© were around 18 or 19. Additional research examining MCI following stroke using the t-MoCA© and detailed neuropsychological testing found that a score cutoff of <19 for MCI on the t-MoCA© was appropriate (Zietemann et al., 2017).

Patient Health Questionnaire – 9 (PHQ-9)

The Patient Health Questionnaire – 9 (PHQ-9) is a depression scale that is short in length, but possesses comparable sensitivity and specificity to other longer measures, and evaluates presence and severity of depression symptoms (Kroenke et al., 2001). The PHQ-9 has been adapted from its original format as a primary care measure, to a telephone-administered measure that can be used in research (Pinto-Meza et al., 2005). The PHQ-9 does not require permission to use, reproduce, or display.

Validity and Reliability

The PHQ-9 demonstrates evidence of criterion-related validity via likelihood ratios between this measure and the likelihood of major depression (Kroenke et al., 2001). The PHQ-9 has demonstrated evidence of excellent reliability with a Cronbach's alpha of 0.89, and strong evidence of test-retest reliability (Kroenke et al., 2001). Intraclass correlation coefficients have been used to evaluate the original version and the telephone-administered version, indicating strong concordance between each version (Pinto-Meza et al., 2005). Internal consistency of the telephone-administered version is close to that of the original version, with overall psychometric properties indicating that the telephone version is reliable for assessing depression (Pinto-Meza et al., 2005).

Interpretation of Score

The PHQ-9 provides data on depression severity, with higher scores indicating more severe depression, via numerically coding responses and adding them up to obtain a total score (Kroenke et al., 2001).

Procedures

Overview

Table 2 summarizes the data collection procedures, including each phase of interaction with the participant. Table 3 summarizes the approximate completion time for each of the measures included in the study. An hour timeslot was scheduled with each participant to allow for ample time to complete the measures.

Table 2

Data Collection Procedure

Initial Recruitment →	Informed Consent Obtained →	Phone Study Session Completed
PI receives portal message response to recruitment message.	PI calls participant to explain the study in depth, review exclusion criteria, and provide information on completing the e-consent.	Once e-consent is completed, an hour-long phone session is scheduled for obtainment of study data. Following this session, the EHR data collection took place.

Notes: PI-Principal Investigator; While the PI is also a member of the transplant team, the participants were informed that the PI was working solely in a research capacity and the information shared would have no impact on their transplantation care.

Table 3

Measure Duration

Measure	Estimated Time to Complete
Demographics and Introduction	10 minutes
t-MoCA©	15 min (Nasreddine et al., 2005)
PHQ-9	3 minutes (Kroenke et al., 2001)
BTACT	20 min (Lachman et al., 2014)
BAASIS©	5 minutes (Dobbels et al., 2010)
Brief IPQ	5 min (Broadbent et al., 2006)

Note: PHQ-9 – Patient Health Questionnaire 9, BAASIS© – Basel Assessment of Adherence to Immunosuppressive Medications Scale, Brief IPQ – Brief Illness Perceptions Questionnaire, BTACT – Brief Test of Adult Cognition by Telephone, t-MoCA© – Telephone Montreal Cognitive Assessment

Access to Potential Participants

After the participant responded to the patient portal recruitment message expressing their interest, the researcher then called them to discuss the research study via a pre-determined script. The participant was informed of the researcher's intention to record the phone assessment for the purposes of analysis. The researcher, who is also a member of the transplant team, informed the participants that the data obtained during the study would not result in any alterations to their care and would be kept confidential from other members of the transplant team. The participant was informed that they can cease participation and withdraw from the research study at any point. For those that agreed to participate, an e-consent was distributed via email for their completion. The participant was then assigned a numeric identifier for privacy protection.

Data Collection

After informed consent was obtained, the phone session occurred at a time agreed upon by the participant and researcher. The session was recorded. At the beginning of the session, the medical/demographic questionnaire was completed and then the measures were applied in the following order: t-MoCA©, PHQ-9, BTACT, BAASIS©, Brief IPQ. The cognitive measures were performed at the beginning of the session to decrease participant fatigue.

Following the phone call study session, the investigator gathered data from the participant's electronic health record (EHR). These data included the immunosuppression medication regimen for the purposes of evaluating laboratory data and obtainment of laboratory trough values for the previous six draws prior to the study date including whether obtained via immunoassay or mass spectroscopy laboratory testing. If participants were undergoing an immunosuppression conversion wherein their regimen was being altered for medical reasons, this was noted for the data analysis. Additional medical variables that were collected from the EHR included the demographic variables of interest as well as past medical history of cardiac arrest, stroke, or mechanical circulatory support device use, to augment patient provided data. It was important to gather both information from the EHR and patient-provided data on these variables as the Mayo Clinic Arizona EHR may not be accurate for individuals that did not receive their transplant at that facility, hence the patient-report was invaluable.

Data Management and Analysis

The PI performed data entry. Study data were collected and managed using REDCap electronic data capture tools hosted at Mayo Clinic (Harris et al., 2019; Harris et al., 2009). All data were entered into de-identified individual electronic worksheets on REDCap (research electric data capture), including data obtained during the application of the measures. Session recordings were used to assist with confirming that accurate information was transcribed for the purposes of scoring. The researcher exported the electronic worksheets into Statistical Package for Social Sciences software (SPSS version 27.0) for analysis. The original REDCap worksheets were compared to the SPSS database entries to confirm accuracy. Initial data analysis included descriptive statistics, including mean, media, mode, and standard deviation.

To evaluate the associations posed in the first aim of the study, point biserial correlations were used to analyze the dichotomous variable of adherent or nonadherent with the other continuous variables. This statistical procedure was also used for the other dichotomous variables that included history of stroke, cardiac arrest, and history of mechanical circulatory support device. Pearson’s correlations were used to examine associations between continuous variables, including duration of mechanical circulatory support device use, illness perceptions, and executive function. To evaluate the relationship between dichotomous variables, for example adherence and history of stroke, Chi-square tests were used.

To analyze the laboratory immunosuppression trough data, the last six immunosuppression concentrations were analyzed using coefficient of variation calculations, with a CV%>30 interpreted as nonadherence (Gustavsen et al., 2019). Importantly, immunosuppression concentrations were analyzed per drug, with participant's that were on multiple drugs that require laboratory trough measurements having each drug immunosuppression concentration analyzed separately.

Logistical regression was used to model the relationship between cognitive test performance, adherence, illness perceptions, and the other statistically significant variables. Logistical regression was used to predict executive function/working memory given previous history with mechanical circulatory support devices.

Protection of Human Subjects

Human Subject Involvement

The purpose of the study was to evaluate relationships between the medication adherence ability of heart transplant recipients and their executive function/working memory, memory processes, illness perceptions, and select medical history components. For this reason, only individuals that had a heart transplant at least six months prior to the study start date were sent a patient portal message, as this time frame ensured that participants were out of the early post-transplant phase wherein they are required to have a caregiver assist with self-management tasks (Myaskovsky et al., 2012). After the participant agreed to being contacted via their response to the portal inquiry, the PI then called the participant to discuss the project, answer all questions, and instruct the participant on how to complete the electronic consent. Following obtainment of informed consent, and hour-long study session phone call was scheduled to complete the study measures. If the participant preferred to complete the hour-long study session phone call immediately following the signing of the e-consent, this was obliged. Following the study session phone call, the participant was thanked for their participation and a phone number was provided should additional questions come up. Following the study session, a $50 check from the Mayo Federal Credit Union was mailed to the participant to thank them for their participation. This remuneration was provided via a grant from the Mayo Clinic Bronfman Endowment for Nursing Excellence.

Data Security

Materials obtained from participants included personal information about medical history and demographics, data from the EHR, and additional information contained within the study measures. The PI recorded and transcribed study data into sequentially coded files that did not contain any identifiers to ensure confidentiality. The PI was the only individual with access to the data, which was stored on a password-protected computer, within password-protected documents/sound files (in the case of the recorded study session). The PI was also the sole owner of a password-protected master-list that included the participant’s name and their corresponding study number.

Potential Risks and Protection Against Risks

Data on medication adherence, including self-report and laboratory data, in addition to data on executive function, memory processes, and prior health conditions (e.g., stroke, cardiac arrest, MCSD) were collected from the EHR. All data were de-identified and password-protected to ensure protection of patient privacy and to prevent identifiable personal information from being inappropriately disclosed. This was especially important given the criteria for re-transplantation that many transplant centers have, in which individuals must have demonstrated adherence to therapies associated with their first transplant. Utilizing the information gathered for research purposes, and not to guide clinical care, was paramount. For individuals that were categorized as moderately or severely depressed on the PHQ-9, or those that reported a positive response to question 9 on the PHQ-9 (thoughts that you would be better off dead or of hurting yourself), the Substance Abuse and Mental Health Services Administration (SAMHSA) Hotline was provided.

Because the study was conducted at the transplant center where the participants receive their usual transplant care, the informed consent process of the research study clearly stated that the recipients did not have to participate to continue receiving standard transplant care. The informed consent also clearly stated that the data collected in the research study would be confidential, and not used to guide medical decision-making. Participants were informed that they had the right to withdraw at any time. Risks associated with in-person meetings during the COVID-19 (coronavirus disease 2019) pandemic were mitigated by conducting the sessions via the telephone.

Potential Benefits

Participants did not individually benefit from participating in the study, however, findings from this study will inform research that seeks to develop effective interventions that result in sustained improvements to medication adherence among heart transplant recipients. Furthermore, information on the executive function/working memory, and memory processes of heart transplant recipients will be foundational to understanding the self-management abilities of heart transplant recipients, especially as life expectancy and age at the time of transplantation increase.

Inclusion of Women and Minorities

Opportunities to participate in this study did not vary based on gender, race, or ethnic status. The only criteria that may have limited the involvement of minorities relates to the need to speak, read, and write in English, based on the measures that were employed.

Results

The manuscript titled *Immunosuppression Medication Adherence Among Heart Transplant Recipients: Relationships with Cognitive Function, Depression, and Illness Perceptions* (Appendix C), provides an overview of the methods and results of this study, including details of the associations between cognitive test performance and medication adherence. This section will provide additional information on the findings from this study, including details that were not included in the manuscript.

Sample Characteristics

Demographic data for the sample are summarized in Table 4. Of the 35 participants, 25 (71.4%) were males, and 10 (28.6%) were females. Most participants (n = 25, 71.4%) were white, married (n = 29, 82.9%), and well-educated, with over 77% (n = 27) having attended some college or more. The average age was 61 years, with a range of 30-75 years. The sample characteristics on gender and race closely mirror the transplant center's overall demographic data, in which 25.8% of total heart transplant recipients were female and 67.9% were white as of January, 2022 (OPTN, 2022). Of the 35 participants, 31.4% (n = 11) were classified as nonadherent, having reported either missing doses of their immunosuppression within the 4-week recall period of the BAASIS© (n = 7), and/or taking medications over two hours before or after their usual dosing time (n = 8). Mild cognitive impairment (MCI) was assessed using the t-

MoCA©, with scores of 19 or above considered normal. Table 5 describes the age characteristics of the participants that scored less than 19 (n = 8).

Table 4

Demographic Characteristics of the Sample

Demographic Characteristics	Mean (SD) or Number (Frequency)
Average Age	61 years (10.3)
Age Range	30-75 years
Gender	
Male	n = 25 (71.4%)
Female	n = 10 (28.6%)
Time Since Transplant	
Less than 1 year	n = 3 (8.6%)
Between 1 and 3 years	n = 9 (25.7%)
Between 3 and 5 years	n = 8 (22.9%)
Between 5 and 7 years	n = 7 (20%)
Over 7 years	n = 8 (22.9%)
Education	
High school graduate/GED	n = 3 (8.6%)
Vocational training	n = 5 (14.3%)
Some or in-progress college/Associate’s degree	n = 13 (37.1%)
Bachelor’s degree	n = 8 (22.9%)
Master’s degree or other post-graduate training	n = 3 (8.6%)
Doctoral degree	n = 3 (8.6%)
Employment	
Employed full-time	n = 9 (25.7%)
Employed part-time	n = 5 (14.3%)
Student	n = 1 (2.9%)
Retired	n = 14 (40%)
On sick leave or disability	n = 5 (14.3%)
Unemployed or temporarily laid off	n = 1 (2.9%)

Table 4 – Continued

Demographic Characteristics	Mean (SD) or Number (Frequency)
Race	
Asian	n = 1 (2.9%)
Black or African American	n = 2 (5.7%)
White	n = 25 (71.4%)
More than one race	n = 3 (8.6%)
Other	n = 4 (11.4%)
Hispanic	
Yes	n = 4 (11.4%)
No	n = 31 (88.6%)
Marital Status	
Single	n = 4 (11.4%)
Married	n = 29 (82.9%)
Divorced	n = 2 (5.7%)
T-MoCA© Category	
Score < 19	n = 8 (22.9%)
Score ≥ 19	n = 27 (77.1%)
PhQ-9 Category	
No depression (score of 0)	n = 5 (14.3%)
Minimal depression (score of 1-4)	n = 17 (48.6%)
Mild depression (score of 5-9)	n = 13 (37.1%)
History of Left Ventricular Assist Device	
Yes	n = 10 (28.6%)
No	n = 25 (71.4%)
History of Documented Cardiac Arrest	
Yes	n = 6 (17.1%)
No	n = 29 (82.9%)
History of Documented Stroke	
Yes	n = 7 (20%)
No	n = 27 (80%)

Table 5

Age Characteristics of the Participants that Scored <19 on the t-MoCA©

Age Range	**Number of Participants that Scored <19 on the t-MoCA©**
41-50 years	n = 1
51-60 years	n = 3
61-70 years	n = 3
71-80 years	n = 1

Correlations: Research Aim 1

Aim 1 of the research study was to examine associations between executive function/working memory, cognitive impairment, illness perceptions, demographic variables, and medication adherence. Table 6 provides details on the correlations between select study variables.

Table 6

Correlations of Select Study Variables

Variables	1	2	3	4	5	6	7	8	9	10	11	12
1. BAASIS©: no missed doses	-											
2. BAASIS©: taking medications on time	**.41***	-										
3. Age	.05	.22	-									
4. Time since transplant	-.13	-.22	.16	-								
5. Education	-.09	-.07	.16	**.39***	-							
6. BTACT immediate word recall	**.42***	.18	-.28	-.31	-.07	-						
7. BTACT immediate word recall intrusions	**-.47****	-.20	-.06	.07	.15	-.40*	-					
8. BTACT delayed word recall intrusions	.28	**-.36***	.19	.06	.20	-.19	.20	-				
9. t-MoCA© delayed memory recall	**.36***	**.34***	.07	.19	.26	**.36***	-.14	-.01	**-**			
10. t-MoCA© total score	.32	**.37***	.01	.13	.15	**.41***	-.12	-.15	**.87****	**-**		
11. PHQ-9 total score	-.18	**-.44****	.05	-.09	.06	-.02	.30	**.36***	-.32	-.21	-	
12. Illness coherence	**.49****	.21	.20	-.21	-.15	.07	-.19	.19	.26	.07	-.18	**-**

Note. BAASIS© = Basel Assessment of Adherence to Immunosuppression Scale; BTACT = Brief Test of Adult Cognition by Telephone; t-MoCA© = Telephone Montreal Cognitive Assessment; PHQ-9=Patient Health Questionnaire 9.
*p<.05. **p<.01

Having no reported missed doses of immunosuppression was associated with higher immediate word recall (r_{pb} = .416, *p* = .013), fewer immediate word recall intrusions (r_{pb} = -.474, *p* = .004), and higher scores on t-MoCA© delayed recall (r_{pb} = .355, *p* = .037). Among those participants who reported missing doses, the frequency with which they missed doses was positively associated with immediate word recall intrusions (r_{pb} = .904, *p* = .005) and higher reported trouble concentrating (r_{pb} = .884, *p* = .008). Participants who reported no missed doses had higher illness coherence scores (r_{pb} = .492, *p* = .003), measured by item 7 on the Brief IPQ (How well do you feel you understand your transplant?). Higher general overall health rating (r_{pb} = .351, *p* = .039) and higher overall satisfaction with health (r_{pb} = .378, *p* = .025) were also associated with reporting no missed doses.

Taking immunosuppression medication on time (e.g., within 2 hours of the usual dosing time) was associated with higher t-MoCA© total scores (r_{pb} = .37, *p* = .03) and t-MoCA© delayed recall scores (r_{pb} = .335, *p* = .049), and fewer delayed word recall intrusions (r_{pb} = -.364, *p* = .032). Those participants that took their medications on time also had lower PHQ-9 total scores, (r_{pb} = -.437, *p* = .009), lower rated frequency on PHQ-9 individual item 6 (feeling bad about yourself) (r_{pb} = -.585, $p < 0.001$), and individual item 7 (trouble concentrating) (r_{pb} = -.361, *p* = .033).

When participants were classified as adherent or nonadherent based on whether they missed doses or took medications over two hours outside of the usual dosing time, adherence was negatively associated with PHQ-9 total score (r_{pb} = -.338, *p* = .047), and positively associated with IPQ7 (r_{pb} = .519, *p* = .001). None of the participants reported that they had altered the prescribed amount of their immunosuppression or that they had stopped taking their medication all together without being advised by their provider to do this. Over 91% of participants (n = 32) rated the importance of their transplant medications on the Brief IPQ as a 10/10, indicating extreme importance.

Of the 35 participants, 32 were on tacrolimus at the time of data collection and had enough laboratory data to calculate a tacrolimus coefficient of variation to indicate trough variability. Unsurprisingly, higher tacrolimus trough variability was negatively associated with adherence cases overall (r_{pb} = -.400, p = .023), and with taking immunosuppression medication on time (r = -.406, p = .021). Higher trough variability was negatively associated with backward digit span performance (r = -.383, p = .031) and trouble falling or staying asleep (r = -.402, p = .023). When trough variability was used to classify participants as nonadherent using tacrolimus trough variability of 30% or higher (Gustavsen et al., 2019), only two individuals demonstrated trough variability above this threshold, with one of those individuals having already been captured as nonadherent by the self-assessment.

There were no significant relationships between medication adherence (measured via self-report or tacrolimus trough variability) and age, time since transplant, education, marital status, or employment status. Having caregiver assistance with organizing medications and/or with remembering to take medications was not significantly associated with self-reported adherence or trough variability. All participants denied missing doses of medications related to an inability to afford their medication. Additionally, no significant relationships were identified with medication adherence and history of cardiac arrest, left ventricular assist device, mechanical circulatory support, or stroke.

Additional associations between demographic variables and the measures utilized were also examined. Age was associated with delayed word recall (r = -0.388, p = 0.021) and category fluency (r = -.395, p = .019). Age was also associated with PHQ-9 item 3 (trouble falling or staying asleep, or sleeping too much) (r = .376, p = .026). Time since transplant was not associated with cognitive test performance, depression, or illness perceptions. Aside from the association with medication adherence, t-MoCA© total score was associated with PHQ-9 item 1 responses (little interest or pleasure in doing things) (r = -.403, p = .01). Having more years of education was associated with lower responses on expected longevity of the transplanted heart measured via Brief IPQ item 2 (how long do you think your transplant will continue or last?) (r = -.555, p <.001) and more correct responses on the red/green nonswitch trials of the BTACT (r = .344, p = 0.043). Marital status was not associated with self-reported adherence or having caregiver assistance with organizing or remembering to take medications. Marital status was associated with responses to Brief IPQ item 8 (how much does your transplant affect you emotionally?) (r_{pb} = -.347, p = .041) with single participants reporting higher scores indicating that they are more emotionally affected.

Caregiver support with organizing and/or remembering to take medications was not associated with self-reported medication adherence or tacrolimus trough variability. Having caregiver support with organizing medications was associated with higher reported frequency of experiencing symptoms on the Brief IPQ (r_{pb} = -.488, p = .003) and lower scores on the MoCA digit span task (r_{pb} = .377, p = .026). This suggests that individuals with challenges related to attention and/or symptoms may be more apt to seek caregiver assistance with medication organization. Interestingly, the individuals that had caregiver support with reminding them to take their medications had higher performance on the number series (r_{pb} = -.345, p = .042) and immediate word recall tasks (r_{pb} = -.408, p = .015). This may indicate that these individuals are using more medication taking strategies (e.g., asking for caregiver assistance with remembering to take medications), despite having higher performance on some cognitive tests than the individuals that are not receiving assistance with reminders.

Correlations: Research Aim 2

Aim 2 was to examine associations between executive function/working memory, cognitive impairment, demographic variables, medication adherence, and history of use of mechanical circulatory support devices, cardiac arrest, and/or stroke. History of mechanical circulatory support devices and/or left ventricular assist device (LVADs), cardiac arrest, and stroke were not associated with tacrolimus trough variability or self-reported medication adherence in this study.

When LVADs were grouped with other forms of mechanical circulatory support or analyzed independently, there were no significant associations identified with medication adherence. Individuals with any form of MCSD were more likely to have had a documented stroke than those without (r_{pb} = .372, p = .028). Having an LVAD specifically was associated with item 2 on the PHQ-9 (feeling down, depressed, or hopeless) (r_{pb} = -.381, p = .024). Having a documented cardiac arrest was associated with lower language fluency scores on the MoCA (r_{pb} = -.470, p = .004).

There were some discrepancies when comparing the participant's self-reported medical history with data from the EHR. All participants with a documented LVAD in the EHR stated that they had an LVAD, but there were differences when comparing the records on stroke and cardiac arrest with participant reports. For instance, six participants had a documented cardiac arrest in the EHR, however 17 participants reported having had a cardiac arrest event prior to transplant and two were unsure if they had experienced this. A documented stroke in the EHR was identified in seven of the participant records, however six participants reported having had a stroke. These discrepancies may be because of confusing medical terminology, for instance some participants talked about mini-strokes or TIAs when describing their history of stroke, while others discussed needing a pacemaker/defibrillator when answering questions about cardiac arrest. This discrepancy could also be because of limited records, particularly for participants that receive post-transplant care at Mayo Clinic but did not receive their pre-transplant heart failure care at this facility. Additionally, the varied experiences and complexity of individuals that have end-stage organ failure and are awaiting transplant may have contributed to this discrepancy given the extreme stress often experienced while awaiting transplant, particularly if patients are requiring advanced therapies in a hospital setting.

Regression: Research Aim 3

Aim 3 was to predict medication adherence using executive function/working memory, cognitive impairment, and history of use of mechanical circulatory support devices. Executive function/working memory were not found to be significantly associated with self-reported medication adherence in this sample and were not able to be established as predictors. Other variables that were shown to be significant were analyzed using logistic regression.

The model using immediate word recall as a predictor of having no missed doses of immunosuppression was found to be the best fit of all the variables, correctly classifying 88.6% of the cases. For every one word increase on the immediate word recall portion of the BTACT, the odds of participants having no missed doses of immunosuppression increased 2.5 times. A logistic regression analysis was also performed to determine predictors of taking medications on time. The model that included PHQ-9 depression total score as a predictor was found to be a good fit, correctly classifying 82.9% of cases. The details of these regression analyses are presented in Table 7. Assumptions of logistic regression were evaluated and met for both models, including testing for linearity of the logit by using a log transformation of the predictor variables.

Table 7

Logistic Regression Results Predicting Medication Adherence

	B	*SE*	*Wald*	*df*	*P*	*Odds Ratio*	*95% CI for odds ratio*	
							Lower	*Upper*
No Missed Doses								
Constant	-4.13	2.19	3.56	1	0.06	.02		
Immediate Word Recall	0.93	0.40	5.46	1	0.02	2.54	1.16	5.55
Taking Meds on Time								
Constant	2.97	0.97	9.44	1	<0.01	19.52		
PhQ-9 Total Score	-0.42	1.80	5.42	1	0.02	0.66	0.46	0.94

Note. R^2 = 0.40 (Nagelkerke) for no missed doses; R^2 = 0.27 (Nagelkerke) for taking meds on time.

Discussion

The purpose of this study was to explore relationships between cognitive function, illness perceptions, and medication adherence among heart transplant recipients. Additional demographic and clinical characteristics were also evaluated. In our sample, 22.9% of participants scored less than 19 on the t-MoCA©, which may indicate MCI (Katz et al., 2021;

Pendlebury et al., 2013). This number is higher than MCI prevalence in the general population (Petersen et al., 2018), particularly when examining the prevalence in the context of participant age; however, is lower than a previous study specific to heart transplant recipients, possibly due to differences in measurement or sample (Burker, Gude et al., 2017). T-MoCA© total scores were not associated with age, education, or history of mechanical circulatory support, LVAD support, stroke or cardiac arrest. Thus, there may be a different pathophysiologic mechanism, for instance prolonged global hypoperfusion associated with heart failure, or impacts from comorbid conditions, which may be involved and warrant further investigation.

Immunosuppression medication nonadherence rates in our sample were consistent with the literature, confirming previous evidence that this population faces substantial challenges related to the implementation phase of medication adherence (Denhaerynck et al., 2018). To our knowledge, this is the first study that examined relationships between cognitive function and medication adherence among heart transplant recipients. While higher tacrolimus trough variability was negatively associated with backward digit span performance in this study, we did not find associations between executive function and self-reported medication adherence. The relationships that were identified between episodic memory, intrusions, and medication adherence represent a novel finding. Episodic memory, measured by word list recall, and inaccurate memory, measured by number of intrusions, may have important implications for the development of medication adherence interventions for this population. Word list recall intrusions occur when a word that was not on the word recall list is produced and have been shown to predict progression to MCI (Thomas et al., 2018), further supporting the possibility that this population is at high risk for developing cognitive impairment. Additionally, heart transplant recipients with MCI may be at risk for medication nonadherence. Incorporating screening for MCI into transplant practices should be considered so that factors contributing to the development of MCI can be addressed. The prevalence of MCI in this population should also be considered when developing interventions designed to support medication adherence.

When considering the relationship between illness perceptions and medication adherence, illness coherence was the only illness perception that was significantly associated with medication adherence. While illness coherence has been defined as an important variable in the literature and was associated with medication adherence in our study, associations with other illness perceptions that have been previously identified in mixed samples of solid organ transplant recipients were not found (Kung et al., 2012). This may be because of differences in perception among individuals that have received different organ transplant types, or because of limitations related to the sample.

In this sample, over 37% of the participants were categorized as having mild depression on the PHQ-9. We found associations between medication adherence, depression, and some specific items on the PHQ-9, indicating that depression, even when mild, was associated with adherence behavior. These results are consistent with the literature, which has identified depression as a predictor of poor adherence in other heart transplant recipient samples (Delibasic et al., 2017). PHQ-9 total scores were not significantly associated with immediate word recall or immediate word recall intrusions in this sample but were associated with delayed word recall intrusions. These results indicate that depression is a psychiatric comorbidity that could influence cognitive function among this group.

Study Limitations

This study has limitations. The cross-sectional design does not allow for causal inferences to be made. The use of a small convenience sample recruited from one transplant center via patient portal limits generalizability. Additionally, only a small number of participants had a history of a left ventricular assist device (n = 10), which likely impacted the results of the analyses that included this variable and limited our ability to draw conclusions about the impact of mechanical circulatory support devices on medication adherence and cognitive function in this population.

The use of patient portal technology for recruitment limited participation by individuals that don’t utilize this technology. While study sessions were conducted via telephone to reduce risk associated with in-person visits during the COVID-19 pandemic, challenges related to telephone administration of measures (e.g., difficulty hearing instructions) may have influenced the findings, although participants were asked to confirm their ability to hear instructions during the session. The telephone format of the study sessions also limited our ability to use cognitive measures that required in-person application. For instance, one of the executive function components of the original MoCA©, the adapted trail making test, is not a part of the t-MoCA© given the need for in-person administration. Limitations related to the use of telephone-based measures may have impacted the findings, particularly as it relates to executive function.

Additionally, the format of the measures did not allow for recruitment of non-English speakers. National data on heart transplantation indicate that white, male individuals have received the majority of heart transplants in the United States of America (USA) (OPTN, 2022), and these demographics were consistent in our sample. However, our sample was less diverse overall than the national data on heart transplantation.

Additional limitations include the use of self-report to capture medication adherence rates, although the adherence rates that were recorded did correspond to previous literature (Denhaerynck et al., 2018). While we used a measure that has been widely used in the transplant literature, self-reporting on behavior represents a complex cognitive task that is highly context-dependent (Schwarz & Oyserman, 2001). The ability to accurately self-report medication adherence relies on memory, and given the associations between adherence, episodic memory, and intrusions identified in this sample, future studies should consider using electronic monitoring methods to further articulate this relationship. Tacrolimus trough variability was used as a secondary measure of adherence, and while the clinical utility of achieving stable plasma tacrolimus concentrations has been established (Gueta et al., 2018), we identified only one additional participant that met criteria for nonadherence based on this measurement.

The cross-sectional nature of the study design did not allow for longitudinal evaluation of medication adherence and cognitive test performance, limiting the ability to understand how these variables may change over time. Some participants that followed at the transplant center for post-transplant care but did not receive their transplantation surgery at the facility had limited records, potentially impacting the ability to draw conclusions based on characteristics of medical or surgical history.

Study Strengths

This is the first study that examined cognitive function and medication adherence among heart transplant recipients and establishes relationships between these variables. Further, the use of valid and reliable measures increases the strength of this study.

Implications for Future Research

The findings from this study indicate that a relationship may exist between episodic memory measured by word list recall, intrusions, depression, illness coherence, and medication adherence among heart transplant recipients. Future research should include longitudinal evaluations of cognitive-test performance, depression, and medication adherence measured using electronic monitoring. These longitudinal studies should include robust neuropsychiatric testing that incorporates cognitive impairment evaluations and depression measures, and thorough analysis of medical/surgical history. This will help to further evaluate the potential relationship between depression and cognitive function in this population and will also allow for a better understanding of the possible mechanisms that may be contributing to cognitive impairment in this group.

Additionally, all interventions that are designed to promote medication adherence in this population need to consider the possibility of cognitive impairment and, converging with other studies, the rate of cognitive impairment (Burker, Gude et al., 2017). This is crucial given the shift towards technology-based interventions that will need to incorporate human factors principles to effectively design for this population.

Educational interventions designed to support heart transplant recipients need to incorporate education on both procedural and memory-based skills that teach the transplant recipient how to effectively take their medications, rather than including only declarative knowledge about the importance of medication. This is important given that over 91% of participants indicated that they believed their transplant medications to be extremely important (10/10 on a Likert scale), however rates of medication nonadherence in this study exceeded 31%, signally a gap between beliefs and knowledge about medications and how to effectively integrate and implement medication-taking in their day to day lives.

Conclusion

Our findings indicate that cognitive impairment may be common among heart transplant recipients, and that cognitive test performance, specifically as it relates to episodic memory, intrusions, and cognitive impairment, may be related to medication adherence in this population. Additionally, important relationships between illness coherence, depression, and medication adherence have also been identified. Future research should include longitudinal evaluation of cognitive test performance, depression, and medication adherence. Additionally, it will be important for future studies to consider the possible predictors of cognitive impairment that may exist in this population, and how this may relate to self-management behaviors and clinical outcomes. As interventions to promote medication adherence increasingly incorporate technology, researchers and developers should consider the unique human factors needs of this population, specifically as it relates to cognitive function.

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APPENDIX A: MANUSCRIPT #1 –

A CONCEPTUAL MODEL ON MEDICATION ADHERENCE AMONG HEART TRANSPLANT RECIPIENTS

A Conceptual Model on Medication Adherence Among Heart Transplant Recipients

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Abstract

Adherence to immunosuppression medications is imperative for optimal health outcomes following heart transplantation; however, nonadherence rates remain high. The purpose of this paper is to describe the process of creating a conceptual model to study medication adherence among heart transplant recipients based on Leventhal's Common-Sense Model (CSM) of Self-Regulation. Theory derivation was used to analyze and modify the concepts and structures in the CSM to better fit the nursing area of interest.

Keywords: medication adherence, heart transplantation, theoretical framework, Leventhal's Common-Sense Model

A Conceptual Model on Medication Adherence Among Heart Transplant Recipients

Heart transplantation is a valuable treatment option that has been shown to improve longevity and quality of life for individuals with end-stage heart failure.[1,2] Receiving an organ transplant requires an ongoing commitment to drug therapy and medical care, rather than the obtainment of a curative state.[3] Despite the importance of adherence to immunosuppression medications following heart transplantation for the prevention of organ rejection and preservation of organ function, medication nonadherence rates remain over 34%.[4] Negative beliefs towards medications are a risk factor for poor adherence among solid organ transplant patients;[5] however, there is a paucity of research regarding how individual perceptions impact decision making processes surrounding medication-taking among heart transplant recipients specifically. Additionally, there is insufficient use of theoretical or conceptual models to explain behavior and perceptions associated with medication adherence following heart transplantation,[3] and this is especially important given the increased desire among the transplant community to develop interventions that will improve adherence. The purpose of this paper is to describe the process of adapting Leventhal's Common-Sense Model (CSM) of Self-Regulation into a conceptual model that can guide research into the medication adherence behaviors of heart transplant recipients.

Leventhal's Common-Sense Model (CSM) of Self-Regulation

The CSM is a framework that can aid in the examination of self-management behaviors and decisions by articulating the process of illness representation formation and action plan development.[6,7] The CSM proposes that people construct illness representations of health threats and procedures for self-management via a dynamic, multi-level process.[7]

Illness representations consist of the domains of identity, timeline, cause, consequence, and control, with these representations ultimately guiding the selection of action plans including illness self-management procedures like medication adherence.[6] While the self is the active agent of self-regulation, the self operates within a larger social context, with self-regulation seen as a process that is dependent upon social, cultural, and environmental factors that can influence the mental representations that ultimately shape self-regulation.[6] The CSM supports the view of a context dependent reality in which illness representation development and change occur as a function of multiple factors.

Application to Heart Transplantation

The CSM is particularly useful for understanding the processes that are involved in the initiation, maintenance, and transition of adherence behaviors through the systematic development of representations that influence procedures for self-management.[7] Perceptions, beliefs, and interpretations of symptoms and information contribute to the formation of mental models that serve as representations of illness threats, ultimately influencing action plan development and behavior.[6,7] Among individuals with asymptomatic chronic conditions, like many organ transplant recipients, there may be a discrepancy between the individual's mental representations and the actual physiologic demands of their transplant,[7] which may influence medication adherence. The representation domains of *timeline* and *consequences* have been identified in solid organ transplant populations, but there is limited research that examines these variables specifically among heart transplant recipients.[8,9] Individual perceptions related to susceptibility to organ rejection are a major predictor of medication adherence among kidney transplant recipients, potentially highlighting the importance of the consequence domain in influencing health-related behavior among transplant patients.[10] Qualitative research indicates that the *timeline* dimension may be especially important to consider in the context of heart transplantation, with uncertainty identified as a common theme, as some individuals feel "healed" and process their heart transplant outside of the context of a chronic disease.[11] These perceptions allude to the mental models that encompass the incorporation of the awareness of health threats, the formulation/organization of behaviors, and subsequent action plan development, operating within a feedback system that continuously evaluates action plan efficacy and progression.[6,7]

While much of the research on illness representations has focused on kidney transplant recipients or samples of mixed solid organ recipients, there may be differences in perception among heart transplant recipients, particularly when considering the impact of cerebral hypoxic injury and potential cognitive function alterations associated with heart transplantation. The clinical course for heart transplant recipients is unique and includes an increased cumulative risk for cerebrovascular injury,[12] which can occur because of acute global hypoperfusion associated with cardiac arrest, acute local hypoperfusion due to stroke or microemboli associated with heart failure and/or mechanical circulatory support devices, or due to prolonged hypoperfusion associated with a low output state from heart failure. One study identified cognitive impairment in 40% of the heart transplant recipients sampled, with cerebrovascular pathology identified in over 30% of those studied.[13] These differences, in addition to overall variances in post-transplant care, necessitate the need for an examination of the self-management behaviors of heart transplant recipients separately from other groups. Adapting Leventhal's CSM via the incorporation of additional concepts, specifically alterations in cognitive function, will provide a conceptual model that can assist with research seeking to examine the self-management behaviors of this particular population.

Adapting Leventhal's CSM Using Theory Derivation

Theory derivation is a strategy that can be used to develop and modify concepts and structures from another discipline to fit within nursing, rather than "borrowing" unchanged theories that may not adequately capture the particular nursing phenomena of interest.[14] This process consists of several steps that include critically examining the literature within nursing and related fields, selecting a parent theory, identifying the content, structure, and concepts within that parent theory, and developing or redefining the concepts to make the theory meaningful for the theorist's field.[14] Leventhal's CSM was identified in the literature as an important health psychology framework that can illustrate the processes by which individuals identify and respond to health threats or stimuli.[7] While this model has provided a framework for the study of various behavioral processes across diverse chronic diseases, modifications were necessary to further explicate the identity domain, and to include additional concepts that may influence the action planning and coping responses of heart transplant recipients.

One example of how theory derivation was used to modify the CSM parent theory is through re-defining the illness representation domain of *identity*, wherein "labels seek symptoms and symptoms seek labels."[6] Identity represents one attribute of illness representations, which encompass the labels that the individual attributes to the associated illness or condition, and their perceptions of the symptoms associated with that illness or condition.[7] The identity component, specifically the symptom labels that individuals attribute to their disease/condition, are likely to evolve over the trajectory of heart transplantation, given the transition from a state of end-stage organ failure to that of a transplant recipient. While the CSM describes stimuli as sensations or deviations from normal function that activate memory processes and mental models of representing the illness,[7] transplantation can represent a dramatic change that results in representation alternations because of new somatic sensations/symptoms, new transplant-related diagnoses, and new environmental and social cues derived from the transplantation experience. Adapting the domain of *identity* to include both the “labels associated with symptoms and characterizations of illness severity” that individuals use as part of illness representation development is more congruent with research that seeks to examine the medication adherence behaviors of heart transplant recipients who may have varying experiences related to their pretransplant illness severity and diverse post-transplant illness characterizations that are not solely related to symptoms.[6]

Development of a Conceptual Model

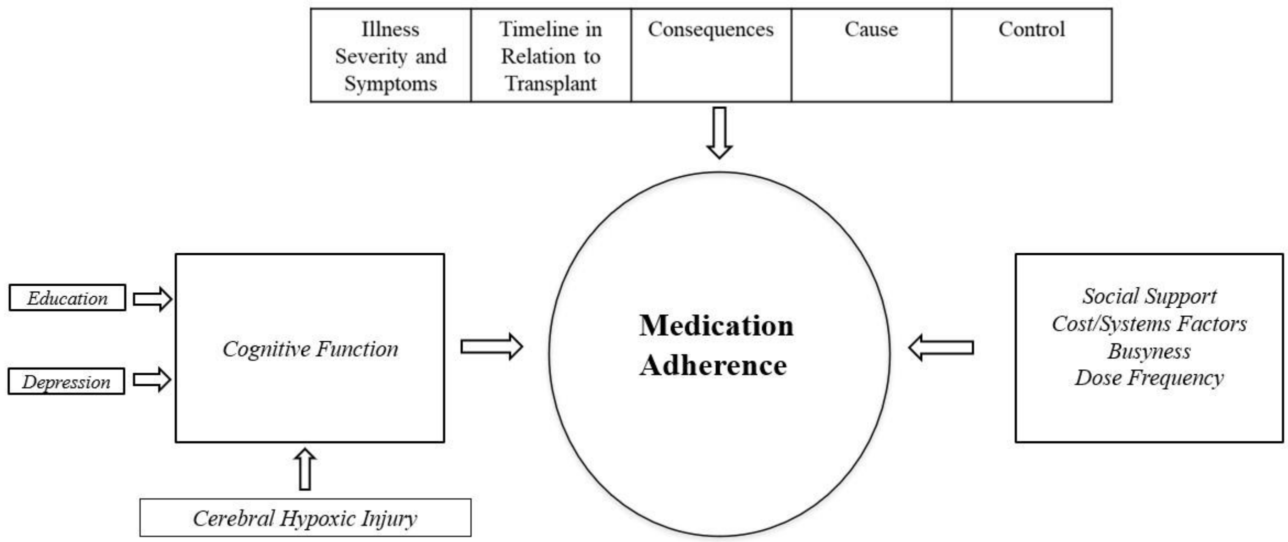
An additional concept of importance that necessitates theory modification for use in heart transplantation is *cerebral hypoxic injury*. Cerebral hypoxic injury as a mechanism that may alter cognitive processes that guide the allocation of resources used during goal-directed behavior, and are responsible for controlling what information about health threats and stimuli reach awareness.[15] These mechanisms are important to consider, with one study finding that 24.3% of heart transplant recipients sampled had a history of cardiac arrest, and 21.6% had a history of cerebral bleeding or infarction.[13] While there is a lack of research into the role of these cognitive processes on the self-management ability of heart transplant recipients, a relationship between executive functions, which assist with perception, decision-making, prioritization, sequencing, and self-regulation, has been established in other chronic diseases.[16-21]

A conceptual model that incorporates illness representation domains from Leventhal's CSM has been expanded to include additional variables that have been shown to be important when considering cognitive function alterations and medication adherence. *Depression* has been shown to influence attention and is associated with significant executive function alterations, particularly those that measure shifting between tasks, inhibition, updating, and working memory.[17,22] *Busyness*, particularly disruptions in routine associated with days of the week,[23] and dose complexity may also play a role in medication adherence.[24] Additional variables that have been proposed to influence adherence among this population, including *education*,[25] *social support*,[26] and *systems factors*,[27,28] have been incorporated into the model.

Figure 1 adapts components of Leventhal's CSM into a model that illustrates the proposed role of illness representations and cerebral hypoxic injury mechanisms in influencing medication adherence in the heart transplant recipient. This model demonstrates the complexity of self-management behaviors in this population and seeks to elucidate the variables that may impact the ability of heart transplant recipients to adhere to their medications.

Figure 1

Conceptual model of the mechanisms contributing to cognitive function alterations and medication adherence in heart transplant recipients



Note. Adapted from Insel (n.d.) Cognitive Enhancement Model for Medication Adherence (CEMMA) and Leventhal et al. (2003) Common Sense Model of Illness Self-Regulation.

Conclusion

Nursing science may draw on theories from other disciplines, however this knowledge must be validated to determine if the generalizations are applicable in nursing and critically analyzed to determine if modifications are necessary.[29] While Leventhal's CSM provides a strong foundation for the study of self-management behaviors among heart transplant recipients, this framework has been adapted to include additional concepts, including cerebral hypoxic injury mechanisms, which may influence medication adherence behaviors. An example of a research question derived from this modified model would be the following: What are the associations/relationships between cognitive processes, illness perceptions, and medication adherence in heart transplant recipients? The formation of this model serves as an important step in guiding nursing research that seeks to examine self-management in heart transplant recipients.

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APPENDIX B: MANUSCRIPT #2 –

EXECUTIVE FUNCTION AND MEDICATION ADHERENCE IN ADULTS: A SCOPING REVIEW

Executive Function and Medication Adherence in Adults: A Scoping Review

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Abstract

Aims and objectives: To identify and examine the literature on executive function and medication adherence in adult chronic disease populations and to make recommendations for future research that seeks to promote medication adherence and self-management of chronic conditions.

Background: Medication nonadherence leads to poorer patient outcomes and increased healthcare costs; however, rates of nonadherence remain high. Medication adherence is a complex, multi-faceted concept and prior research indicates that this behavior involves higher order cognitive processes that include executive function.

Design and Methods: The Arksey & O'Malley framework for conducting scoping reviews was utilized in addition to the PRISMA-ScR checklist. PubMed was used to identify relevant research published since 2000, from which we extracted 28 publications that focused on medication adherence and executive function, summarizing the contents for this review.

Results: Executive function has been found to be a predictor of medication adherence among individuals with HIV. There is evidence that a relationship exists between executive function and medication adherence across a diverse range of chronic disease states that include benign prostatic hyperplasia (BPH), overactive bladder, stem cell transplantation, early-stage breast cancer, heart failure, diabetes, asthma, chronic obstructive pulmonary disease (COPD), and among older adults taking prescribed medications.

Relevance to Clinical Practice: A relationship between executive function and medication adherence has been identified in several chronic disease states and among older adults; however more research is needed to examine this relationship across additional populations. Incorporating

knowledge about executive function processes will be important for future nursing intervention development that seeks to promote self-management behaviors like medication adherence.

Keywords: medication adherence, executive function, self-management, cognitive function

Executive Function and Medication Adherence in Adults: A Scoping Review

Medication adherence is multifactorial and is described as an alignment between an individual's behavior and their prescribed medication dosing regimen (Gast & Mathes, 2019; Sabaté, 2003). Despite the importance of adherence for the management of chronic disease and achievement of optimal health outcomes, rates of nonadherence are estimated to be around 50% (Chisholm-Burns & Spivey, 2012; Sabaté, 2003). While medication adherence is multifaceted and can be influenced by systems-level factors like cost or access to medications, and patient-level factors like self-efficacy, attitudes/norms, and motivation, cognitive factors may also influence the ability to adhere to medications (Insel et al., 2006). Medication adherence relies on cognitive processes that include executive functions, as individuals must develop and adapt a plan for adherence, encode the intention to take the medication as prescribed, store this information, remember to take the medication at the correct time, and continuously monitor whether the medication was taken as intended (Insel et al., 2006). Health care professionals may not be aware of the importance of these cognitive processes, specifically executive function, when caring for people managing diseases that require medications (Schillerstrom et al., 2005). Better understanding of the relationship between executive function and medication adherence behaviors could enhance the nurse's ability to educate and develop interventions to support self-management among individuals with chronic illness.

Executive functions consist of the higher-level skills used in the organization and regulation of behaviors (Miyake & Friedman, 2012; University of California San Francisco, n.d.). This broad term is used to capture the cognitive processes involved in updating working memory, allowing for quick retrieval of task-relevant information (Hofmann et al., 2012; Miyake et al., 2000). Executive functions also include the ability to shift or switch back and forth between multiple mental tasks (Hofmann et al., 2012; Miyake et al., 2000). Medication adherence includes the ability to adjust schedules when plans change, plan for the availability of medications, and remember to pick up medications from the pharmacy (Stilley et al., 2010). The role of prospective memory processes, or remembering to do something you intend to do in the future (e.g. take medications) depends on executive function (Martin et al., 2003). The initiation of action plans to achieve goals, the direction of attention to goal-oriented information, and the ability to flexibly switch between different tasks are mechanisms of self-regulation that are required for medication adherence, and are thought to be heavily influenced by executive functions (Hofmann et al., 2012).

There is evidence that a variety of medical illnesses may impact cognitive function, in particular the domain of executive function (Hedges, 2019). Executive function deficits have been assessed following acute illnesses, including after COVID-19 infection, potentially contributing to the cognitive difficulties of COVID-19 “long-haulers” (Miskowiak et al., 2021), and increasing the relevancy of understanding the relationship between executive function and medication adherence. There is also evidence that executive function deficits are related to cognitive changes seen during cancer treatment, sometimes referred to as “chemo brain” or “brain fog” (Vannorsdall, 2017). Despite the extensive literature on executive function and chronic diseases, a review on the relationship between executive function and medication adherence has not been performed. An examination of the literature on executive function and medication adherence is needed to guide nursing research that seeks to promote the medication adherence of individuals suffering from chronic illnesses.

Aims

The purpose of this scoping review is to identify and examine the research on executive function and medication adherence in adult chronic disease populations.

Methods

The Arksey and O'Malley (2005) framework for conducting scoping reviews was utilized, wherein a question was generated, relevant studies were identified and selected, and a summarization of the results was completed. Scoping reviews assist with illustrating and summarizing literature in a field of interest, making this approach appropriate to achieve the study aims (Arksey & O'Malley, 2005). This review is not associated with a pre-existing protocol or a funding source, and the search did not provide evidence of similar reviews on this topic. This review addressed the following question: Is there a relationship between medication adherence and executive function in adult chronic disease populations?

Search Strategy and Eligibility Criteria

The search was conducted using the database PubMed and was limited to articles published in English since 2000. A search consisting of “medication adherence” AND “executive function” was conducted to evaluate literature in populations where the role of executive function in medication adherence has been examined. While medication adherence is the preferred Medical Subject Heading in the National Library of Medicine, a literature search using the keywords “medication compliance” AND “executive function” was also conducted to capture literature that may have used this term. The results from this search were cross-referenced with the original search on medication adherence to screen for duplicative articles or those not meeting inclusion criteria, ultimately resulting in one additional study that was included in the review.

The articles that were retained for summarization focused on medication adherence and executive function or domains of cognitive function. Articles that focused on dementia, Alzheimer's Disease, or neurodegenerative diseases were excluded, given that these diseases require unique consideration for behaviors like medication adherence and may not allow for self-management of medications. Articles that were focused on psychiatric disorders were also excluded given the potential impact of these conditions on cognitive function. Articles on pediatric populations were also excluded given that the focus of this review is on adults with chronic diseases. Articles that did not focus on some component of cognitive function and medication adherence were also excluded. Articles were included regardless of study design; however, conference proceedings, case studies, measure validation studies and editorials were excluded. Following the search, the first author read the title and abstract of each article to identify whether inclusion criteria were met, followed by additional analysis of the full-text articles (Figure 1).

Results

Table 1 provides details on the studies that were included (n = 28), which represent a limited but diverse range of chronic disease conditions. The literature on HIV provided initial evidence articulating the role of executive function in adherence, with executive function found to be strongly predictive of medication adherence in this population (Ettenhofer et al., 2010; Hinkin et al., 2002). HIV positive individuals with neurocognitive impairment were found to have 2.5 times greater risk of nonadherence when compared with those that had normal cognitive performance (Hinkin et al., 2004). Prospective memory was found to be a predictor of nonadherence among individuals who are HIV positive (Contardo et al., 2009; Zogg et al., 2010). Cognitive processes among HIV positive individuals have been shown to impact medication management independent of age, with executive functioning and the additional cognitive domains of verbal fluency, learning/memory, and spatial reasoning associated with performance on a medication management measure (Thames et al., 2011).

Executive function predicts medication management behaviors among individuals who received stem cell transplantation and those with early-stage breast cancer, providing further evidence as to the role of executive function in medication adherence across a broad spectrum of disease processes (Mayo et al., 2016; Stilley et al., 2010).

Among individuals with heart failure and concurrent atrial fibrillation, a qualitative narrative analysis was used to evaluate patient and provider perceptions of anticoagulation adherence. Results indicate that patients and their providers consider cognitive function to be an important factor in treatment adherence to anticoagulation (Ferguson et al., 2017). Medication management skills among older adults with heart failure are compromised in individuals with cognitive impairment, particularly in relation to errors of omission (Howell et al., 2017). Poorer cognitive function, particularly memory performance, is associated with worse medication adherence among community-dwelling patients with heart failure although executive function specifically is a predictor only before adjusting for other variables (Dolansky et al., 2016). Performance on attention, executive function, and language measures have been associated with poorer overall adherence to self-care behaviors among older adults with heart failure further articulating the role of cognitive processes in treatment adherence among this population (Alosco et al., 2012).

Among heart failure patients awaiting transplantation, alterations to executive function were common; however the relationship between cognitive dysfunction and self-management behaviors was not demonstrated and it is unclear if executive function improves with the attainment of normal hemodynamics following transplantation (Mapelli et al., 2011). In kidney transplantation, findings associating cognition and adherence are mixed. One study found that neurocognitive ability may have an indirect role in medication adherence via self-efficacy and depression (Paterson et al., 2018), with everyday problem solving measures found to be predictive of adherence when traditional neuropsychological tests were not (Gelb et al., 2010). While everyday problem solving measures do not directly measure executive function, they are considered to be supportive of analytical problem solving, via the maintenance, retrieval, planning, and monitoring of tasks and goals (Wiley & Jarosz, 2012). In considering medication knowledge, there is evidence that kidney transplant recipients with mild cognitive impairment, classified using the Mini-Mental State Examination (MMSE), scored significantly lower on measures of treatment knowledge (Patzer et al., 2016). Older kidney transplant recipients in particular have high rates of forgetting medications (30%) even in samples that excluded those with cognitive limitations, suggesting that actual rates of nonadherence may be much higher and indicating a need to generate research that examines both cognition and medication adherence in this population (Tielen et al., 2011). In liver transplantation, an association between cognitive processes and medication adherence has not been elucidated, with no evidence of a relationship between cognition and self-management behaviors (Ko et al., 2019) including medication adherence (Serper et al., 2015). The majority of the studies that included some aspect of cognitive function when considering transplant recipients were focused on cognition as a component of behavioral interventions or mobile technology affinity rather than on assessments of cognition as it relates to medication adherence (Berben et al., 2011; De Bleser et al., 2009; Reber et al., 2018; Senft et al., 2017). Two of these studies were descriptive, with aims that included the evaluation of practice patterns to improve adherence among transplant centers and medication adherence among older adults with heart failure (Howell et al., 2017; Senft et al., 2017).

In 5 studies, better executive function was associated with medication or medical treatment adherence over a range of chronic disease conditions, including benign prostatic hyperplasia (BPH), overactive bladder, diabetes, asthma, and chronic obstructive pulmonary disease (COPD) (Caballero et al., 2018; Kosilov et al., 2019; Kosilov et al., 2020; O'Conor et al., 2019; Tomlin & Sinclair, 2016). Executive function has been identified as a predictor variable that significantly influences adherence among older men with BPH and overactive bladder, and older women with overactive bladder (Kosilov et al., 2019; Kosilov et al., 2020). A relationship between executive function and medication adherence has also been identified among Hispanic older adults with diabetes mellitus (Caballero et al., 2018). Measures of executive function and memory are associated with adherence to diabetic medications among older adults with diabetes, with one study finding perceived executive function to be a significant predictor of hemoglobin A1c (Cuevas & Stuifbergen, 2017; Tomlin & Sinclair, 2016). Among older adults with asthma, working memory, processing speed, and executive function (characterized as fluid abilities) were strongly related to health literacy and were associated with proper inhaler administration techniques (O'Conor et al., 2015). These fluid abilities are also associated with medication behaviors among individuals with COPD (O'Conor et al., 2019). In older adults, better executive function is associated with medication adherence and executive dysfunction is associated with increased risk for hospital readmissions (Anderson & Birge, 2016; Insel et al., 2006; Stoehr et al., 2008).

Discussion

The results of this scoping review demonstrate that a relationship between executive function and medication adherence has been identified in several chronic disease states. Among older adults, an intervention that included consideration for cognitive processes during design was effective at improving adherence when compared to simple educational initiatives (Insel et al., 2016). Together these findings suggest there is a strong need for further analysis into the role that cognitive processes have on medication adherence, with specific focus on the role of executive function in this self-management behavior, and consideration for how to incorporate this science into intervention development.

Additionally, future research that seeks to examine cognitive processes and medication adherence should apply measures that incorporate executive function into their assessment and report findings specific to individual cognitive domains. Differences in measurement were common in the literature that we reviewed, with some articles only reporting on cognitive impairment or overall cognitive processes rather than the specific cognitive domains that have been associated with medication adherence. While this review focused on the relationship between executive function and medication adherence, it is also important to note that differences in the measurement and definition of medication adherence may also impact this relationship, and future research should incorporate robust adherence measures into design.

This scoping review identified several studies that examined executive function and medication adherence among individuals with diverse chronic diseases. A limitation of this review is that the focus on executive function as a keyword may have excluded research studies that examined executive function as part of overall and more generic measures of cognitive function. Many of the research studies that were included were published in medical, pharmacy, or psychology journals, further re-enforcing the need for an examination into executive functions and self-management behaviors like medication adherence from a nursing perspective.

Conclusion

This scoping review explored the evidence on executive function and medication adherence in the chronic disease literature; however, additional research is needed to evaluate this relationship across broader populations. The use of cognitive measures that evaluate executive function, and consideration for cognitive processes in intervention development should be considered when designing research that seeks to evaluate or promote medication adherence among individuals with chronic diseases.

Relevance to Practice

Nurses are largely responsible for providing education to individuals with complex diseases from diagnosis to ongoing management, across a variety of environments that include hospitals, ambulatory care, and home care settings. There is increasing evidence to suggest that education alone is not sufficient to support self-management behaviors and including strategies that support executive function has the potential to improve medication adherence. Implications for the development of nursing interventions must extend beyond simple educational initiatives or reminders to promote optimal health among chronic disease populations. While additional research is needed, consideration for executive function can be incorporated into nursing research that examines relationships with medication adherence and intervention development to support self-management among those with chronic diseases.

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Figure 1

PRISMA flow diagram of identified literature

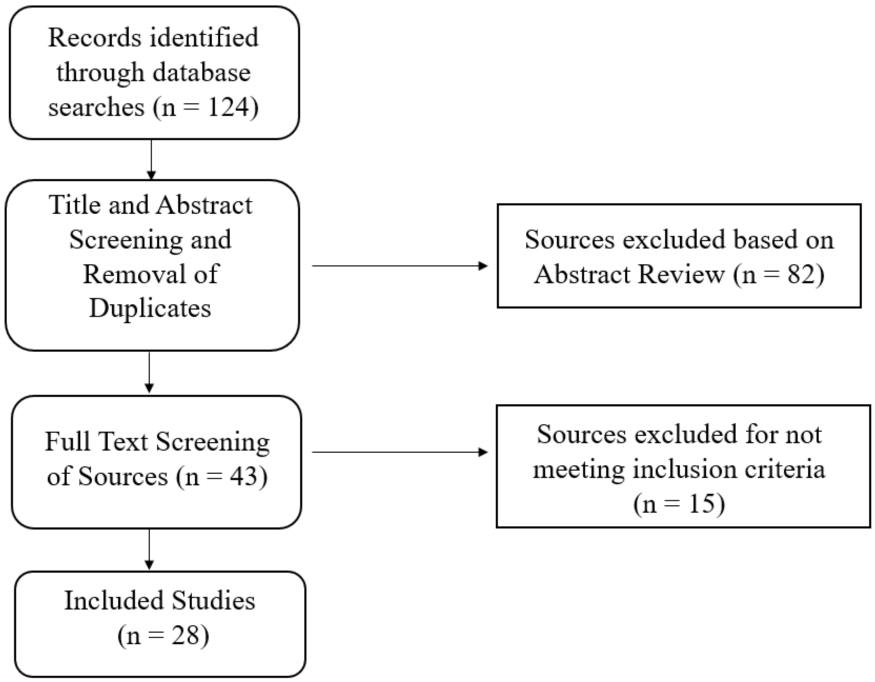

Table 1

Characteristics of Included Articles in the Scoping Review of Literature on Executive Function and Medication Adherence (n= 28)

First author, year	Chronic Disease	Sample	Design	Purpose	Findings
Alosco, 2012	Heart Failure	N= 149	Descriptive, Cross-sectional	To explore the relationship between cognitive impairment and reported treatment adherence.	Cognitive function is an independent contributor to medication adherence, with reduced performance on attention, executive function, and language measures associated with poorer overall adherence.
Anderson, 2016	Older Adults	N= 452	Prospective, Observational	To examine executive function as a risk factor for early readmission in older adults discharged from the hospital.	Executive function alterations were a risk factor for readmission in older adult individuals managing their own medications.
Caballero, 2018	Diabetes Mellitus; Hispanic; Older Adults	N= 40	Descriptive, Cross-Sectional	To investigate the relationship between cognitive variables, demographic variables, and medication nonadherence	Executive control function, as measured by the CLOX 1 instrument, was related to self-reported medication adherence.

				among older Hispanic adults with type 2 diabetes.	
Contardo, 2009	HIV	N= 97	Prospective, Observational	To evaluate the factor structure of a test battery that included the MIST (memory for intentions screening test). To determine whether factors on the MIST or other tests were associated with medication adherence.	One factor, a MIST factor, was significantly correlated with adherence, distinguishing the MIST factor from traditional memory function assessments, and indicating a relationship between prospective memory and adherence.
Cuevas, 2017	Diabetes Mellitus	N= 120	Descriptive, Cross-Sectional	To examine the perceptions of a diverse sample of individuals with type 2 diabetes, specifically as it relates to cognitive ability.	Executive function scores were positively associated with dietary adherence and blood glucose monitoring, with executive function found to be a significant predictor of A1C.
Dolansky, 2016	Heart Failure	N= 309	Prospective, Observational	To evaluate the impact of cognitive function on medication adherence in a sample of	Poorer cognitive function, particularly memory performance, is associated with worse medication

				individuals with heart failure.	adherence among community-dwelling patients with heart failure although executive function specifically is a predictor only before adjusting for other variables.
Ettenhofer, 2010	HIV	N= 91	Prospective, Cohort	To evaluate whether cognitive ability is predictive of medication adherence.	Of all variables included in the neuropsychological evaluation, executive function and learning/memory were most strongly predictive of levels of medication adherence achieved.
Ferguson, 2017	Heart Failure; Atrial Fibrillation	N= 144	Qualitative, Narrative Inquiry	To evaluate the perspectives of patients and providers as it relates to barriers and enablers of adherence to anticoagulation in individuals with heart failure with atrial fibrillation (AF).	Cognitive impairment was considered one of the key barriers to anti-coagulation adherence.
Gelb, 2010	Kidney Transplant	N= 108	Descriptive, Cross-Sectional	To apply traditional and everyday	Higher depressive symptoms and

				cognitive measures to predict medication adherence among kidney transplant recipients.	worse performance on the everyday problem-solving test were predictive of poorer self-reported medication adherence.
Hinkin, 2002	HIV	N= 137	Prospective, Observational	To evaluate neuropsychological compromise and regimen complexity in HIV positive adults and to determine whether this is predictive of poor medication adherence.	Individuals that had cognitive compromise and more complex regimens had poorer adherence. Poor adherence was associated with executive function, memory, and attention deficits.
Hinkin, 2004	HIV	N= 148	Prospective, Observational	To assess predictors of medication adherence among HIV-positive individuals.	Individuals that were older were more likely to be adherent. Participants with neurocognitive impairment had a 2.5 times greater risk of being rated as a poor adherer. Executive function deficits were associated with poor adherence.

Howell, 2017	Older adults, Heart failure	N= 55	Descriptive, Cross-Sectional	To evaluate the cognition and medication self-management skills of consecutive older adults hospitalized for heart failure.	Cognitive impairment was associated with poorer medication management skills. Participants with cognitive impairment had more errors of omission, however executive function was not clearly evaluated.
Insel, 2006	Older adults, Hypertension	N= 95	Prospective, Observational	To examine associations between cognitive function and medication adherence in older adults.	The only significant predictor of medication adherence was the composite of executive function and working memory.
Ko, 2019	Liver Transplant	N= 113	Descriptive, Cross-Sectional	To explore self-management behaviors and relationships between self-efficacy, health information seeking behavior, and cognition among liver transplant recipients.	While liver transplant recipients demonstrated evidence of mild cognitive impairment, this was not related to self-management.
Kosilov, 2019	Older females,	N= 417	Descriptive, Cross-Sectional	To evaluate the relationship between	Predictors that significantly influenced

	Overactive Bladder			executive function and working memory on adherence among older women with overactive bladder.	medication adherence were executive function and a composite of working memory, as well as severe symptoms and age.
Kosilov, 2020	Older men, Benign Prostatic Hyperplasia, Overactive Bladder	N= 395	Descriptive, Cross-Sectional	To evaluate the relationship between executive function and working memory on treatment adherence in older men with BPH.	Predictors that significantly influenced adherence were executive function and a composite of working memory, as well severe symptoms, and age.
Mapelli, 2011	Heart Failure, End-Stage Heart Disease	N= 207	Descriptive; Cross-Sectional	To describe the cognitive profiles of individuals with end-stage heart disease.	The executive function domain was the domain that was most impaired, however researchers did not examine relationships between cognitive performance and medication adherence.
Mayo, 2016	Stem Cell Transplantati on	N= 77 at baseline, 58 at first follow	Prospective, Observational	To evaluate the relationship between neurocognitive performance and	Neurocognitively impaired individuals had worse performance on

		up session, and 41 completed all study sessions		medication management among stem cell transplant recipients within the first 6 months after transplant.	medication management tasks. Worse performance on executive function and working memory measures predicted impaired medication management.
O’Conor, 2019	Chronic Obstructive Pulmonary Disease	N= 393 at baseline, 333 at one year, and 299 at two years	Prospective Cohort	To explore relationships between health literacy and cognitive ability with self-management behaviors.	In addition to adequate health literacy, fluid abilities (processing speed, working memory, long-term memory, executive function) were also associated with medication behaviors.
O’Conor, 2015	Older adults, Asthma	N= 425	Descriptive, Cross-Sectional	To evaluate relationships between cognitive skills, health-literacy, and asthma-related medication use among older adults with asthma.	Fluid abilities (working memory, processing speed, executive function) were associated with medication behaviors, as was limited literacy. Literacy associations were reduced when fluid abilities were incorporated into the multivariate model.

Paterson, 2018	Renal Transplant Recipients	N= 211	Descriptive, Cross-Sectional	To model relationships between cognitive abilities, depression, self-efficacy, and medication adherence among renal transplant recipients.	Adherence was positively associated with self-efficacy and everyday problem solving. Neurocognitive abilities were positively associated with self-efficacy but not directly related to adherence.
Patzer, 2016	Renal Transplant Recipients	N= 99	Descriptive, Cross-Sectional	To examine associations between medication understanding and non-adherence.	Renal transplant recipients with mild cognitive impairment had lower treatment knowledge scores.
Serper, 2015	Liver Transplant Recipients	N= 105	Descriptive, Cross-Sectional	To examine medication understanding, medication adherence, and clinical outcomes in liver transplant recipients.	While 12% of participants were identified as meeting criteria for mild cognitive impairment, this was not directly related to adherence.
Stilley 2010	3 studies: Hyperlipidemia Diabetes Mellitus Early-Stage Breast Cancer	N= 581	Prospective; Observational (Breast Cancer); Randomized Control Trial (Diabetes, Hyperlipidemia)	To compile 3 studies that seek to examine cognitive function and medication adherence.	Attention/mental flexibility, and/or working memory deficits were a predictor in all studies. In 1 study, poorer executive function performance was

					related to poor adherence.
Stoehr, 2008	Older Adult Primary Care	N= 343	Descriptive, Cross-Sectional	To examine associations between cognitive domains and medication management.	Better performance on executive function measures was strongly associated with medication adherence, while verbal memory functioning was associated with setting up a medication schedule.
Thames, 2011	HIV	N= 51	Descriptive, Cross-Sectional	To examine relationships between aging, cognitive impairment, medication management, and financial management among an HIV positive sample.	No relationship between laboratory performance and self-reported medication management was found, however executive functioning and the additional cognitive domains of attention/working memory, verbal fluency, learning/memory, and spatial reasoning were associated with medication management in older participants.

Tomlin, 2016	Diabetes Mellitus	N/A	Systematic Review	To investigate the literature on diabetes and self-management.	Twelve studies were included. Authors concluded that older diabetic people are at increased risk for cognitive dysfunction, and that cognitive changes may affect diabetes self-management behaviors.
Zogg, 2010	HIV	N= 139	Semi-naturalistic design	To evaluate prospective memory as a predictor of compliance failures, with a task meant to mimic “real-life” circumstances.	Prospective memory was a significant predictor of noncompliance after controlling for confounders.

APPENDIX C: MANUSCRIPT #3 –

IMMUNOSUPPRESSION MEDICATION ADHERENCE AMONG HEART TRANSPLANT RECIPIENTS: RELATIONSHIPS WITH COGNITIVE FUNCTION, DEPRESSION, AND ILLNESS PERCEPTIONS

Immunosuppression Medication Adherence Among Heart Transplant Recipients: Relationships with Cognitive Function, Depression, and Illness Perceptions

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Abstract

Background and Purpose: There is a paucity of research that examines the relationships between cognitive function, illness perceptions, and immunosuppression medication adherence among heart transplant recipients. The purpose of this study is to describe these relationships, as this knowledge is necessary to improve adherence-promoting interventions and post-transplant care.

Methods: A cross-sectional, observational design was used. Measures evaluated cognitive test performance, self-reported medication adherence, depression, and illness perceptions. We also collected sociodemographic data and data from the electronic health record on tacrolimus trough variability and medical/surgical history.

Results: Of the 35 participants that were included, 31.4% (n = 11) were classified as nonadherent. Individuals with no reported missed doses of immunosuppression had higher immediate word recall, fewer word recall intrusions, and higher illness coherence scores. Taking medications on time was associated with higher t-MoCA total scores and memory recall scores, fewer delayed word recall intrusions, and lower overall depression scores. In our sample, 22.9% (n=8) of participants scored less than 19 on the t-MoCA, which may indicate Mild Cognitive Impairment (MCI). Immediate word recall was determined to be a predictor of having no missed doses of immunosuppression, while PHQ-9 total score was found to be a predictor of taking medications on time.

Conclusion: Our findings indicate that cognitive impairment may be common among heart transplant recipients. Cognitive test performance, specifically as it relates to episodic memory, intrusions, and cognitive impairment, may be related to medication adherence among this

population. Illness coherence and depression were identified as additional variables of importance. Consideration for these relationships is needed when designing interventions to promote adherence among this population, and additional research should consider longitudinal evaluation of cognitive function and medication adherence in this group.

Immunosuppression Medication Adherence Among Heart Transplant Recipients: Relationships with Cognitive Function, Depression, and Illness Perceptions

Heart transplant recipients experience extreme medical vulnerability, characterized by transplant-related risks that include organ rejection, malignancy, and infection, in addition to high rates of other chronic diseases (McCartney et al., 2017). Neurologic complications, particularly those associated with stroke and/or mechanical circulatory support devices, can have implications for the cognitive function of this population (Cupples & Stilley, 2005), with recent research indicating that a substantial portion of heart transplant recipients meet criteria for mild cognitive impairment (Burker, Gude et al., 2017; Burker, Gullestad et al., 2017). There are several mechanisms through which heart transplant recipients can experience cerebral hypoxic injury that may impact cognitive processes, including acute global brain ischemia associated with cardiac arrest, prolonged hypoperfusion associated with heart failure, and/or acute focal ischemia associated with stroke or microemboli, particularly in the setting of mechanical circulatory support devices. These complications may be compounded by increasing age at the time of transplant (Colvin et al., 2018), and well described age-associated cognitive changes (Salthouse, 2019).

These mechanisms may have significant implications for self-management behaviors like medication adherence. Heart transplant recipients require lifelong immunosuppression medication in order to protect the transplanted organ from immunologic injury and graft failure (Dobbels et al., 2004; McCurry, 2019); however, despite educational efforts, medication nonadherence rates remain as high as 34.1% (Denhaerynck et al., 2018). Medication nonadherence is associated with a greater incidence of clinical events that include the development of transplant-related coronary artery disease and acute organ rejection (Denhaerynck et al., 2018; Dobbels et al., 2004), necessitating a need to consider the role that cognitive factors may have on adherence in this population. Medication adherence is multifactorial (Gast & Mathes, 2019; Sabaté, 2003) and represents a complex behavior (Insel et al., 2006), with tasks such as adjusting to schedule changes, planning for the availability of medications, and remembering to pick up medications from the pharmacy requiring individuals to encode and store the intention to take the medication and to retrieve this information at the correct time (Stilley et al., 2010). These memory processes represent the individual's cognitive ability to create, manage, and execute the medication-taking intention at the appropriate time in the future, and are an important component of medication adherence (Zogg et al., 2011).

In a study on long-term survivors of heart transplant, 39% displayed impaired test performance, especially on cognitive tests that measured memory, processing speed, language, and executive function (Burker, Gude et al., 2017). Executive functions consist of cognitive control processes that assist with perception, decision-making, prioritization, sequencing, and self-regulation (Miyake & Friedman, 2012; Snyder et al., 2015), with previous research providing evidence to support that a relationship exists between executive function and medication adherence across a wide range of chronic disease states (Alosco et al., 2012; Ettenhofer et al., 2010; Hinkin et al., 2002; Insel et al., 2006; Mayo et al., 2016; Stilley et al., 2010). There is also evidence that even small cognitive changes can have a negative impact on medication adherence in other populations (Hayes et al., 2009). While nonadherence among transplant recipients is associated with both intrinsic/patient-related factors, and extrinsic factors (Denhaerynck et al., 2018), there is a paucity of research examining the relationship between cognitive function and adherence (Cupples & Stilley, 2005). Additionally, while the role of illness perceptions has been explored in mixed groups of solid organ transplant recipients (Kung et al., 2012), there is a need to explore how perceptions and beliefs may influence adherence in heart transplant recipients specifically, particularly in the context of cognitive function. The purpose of this study is to describe the relationships between cognitive function, illness perceptions, and medication adherence among heart transplant recipients with the goal of expanding insights into factors associated with nonadherence to immunosuppression.

Design/Methods

Design

A descriptive, cross-sectional design was used to examine associations between the variables of interest. Leventhal's Common-Sense Model (CSM) of Self-Regulation has been adapted to provide the conceptual foundation for this research, wherein individuals produce representations of their illness which influence self-management procedures, the formulation/organization of behavior, action plan development, and appraisals of progression and past behavior (Leventhal et al., 2003; Leventhal et al., 2016).

Setting

This study took place at the Mayo Clinic Arizona Transplant Center, which is home to a medium-sized heart transplantation program and manages the care of over 400 heart transplant recipients. Approval to conduct this study was obtained from the Mayo Clinic Institutional Review Board.

Study Sample

Recruitment for the convenience sample occurred via electronic health record patient portal message requests. Portal messages were sent to adult (e.g., >18 years old) heart transplant recipients that were over six months past their transplantation surgery. This criterion was based on the transplant center's requirement that individuals have a caregiver in the early post-transplant period to assist with self-management behaviors like medication adherence, and the transplant center's medication weaning protocol wherein individuals are retained on higher doses of corticosteroids that may impact cognitive test performance for the first few months following transplantation.

After interested individuals responded to the portal message, they were called to review study details and were screened to ensure that they met additional inclusion criteria. Participants had to be able to read, write, and understand English given the format of the measures. Individuals with a diagnosis of dementia were excluded, as were those with active substance abuse, given the impact of these conditions on cognitive function. Individuals who were not independently managing their own medications, for instance those that were completely reliant on a caregiver or that lived in a facility that administered their medications, were also excluded during the initial screening call. Women who were pregnant or attempting to become pregnant were excluded, as were individuals that were admitted to the hospital during data collection, given that they would not be independently managing their medications during hospitalization. Following this initial recruitment call and screening, informed consent was obtained electronically from the participants that were interested in moving forward. Individuals continued to be recruited, on a rolling basis, until the goal sample size was achieved.

Using G*Power 3 software, a sample size of at least 34 was targeted based on previous research indicating that this sample size allows for the detection of small differences in cognitive function of one standard deviation, with required power of 0.8 and level of significance of .05 (Burker, Gullestad et al., 2017). After the initial screening and informational phone call, 35 participants consented to proceed with the study. There were 2 individuals that did not to take part after the initial screening and informational session. One individual read the consent and chose not to participate, and we were unable to get back into contact with the other individual to schedule the study session after the initial screening call.

Data Collection and Measures

After informed consent was obtained, a one-hour phone study session was conducted. Phone sessions were used to decrease risk associated with in-person visits during the COVID-19 pandemic, and to ensure that individuals living outside of the urban area surrounding the transplant center were able to participate.

Demographic Information

A demographic questionnaire was administered at the beginning of the study session. Following the session, additional information, including history of stroke, cardiac arrest, and/or mechanical circulatory support device information was obtained from the electronic health record. Laboratory trough data for the participant’s last six lab draws was also obtained to be used as a secondary measure of medication adherence via trough variability calculations (Gustavsen et al., 2019).

Telephone Montreal Cognitive Assessment (t-MoCA©)

The Montreal Cognitive Assessment is widely recognized as an effective measure to assess for milder forms of cognitive impairment, and the telephone-adapted version allows for the administration of this measure except for the visuoexecutive and naming components (Castanho et al., 2014). Pendlebury et al. (2013) found that optimal sensitivities and specificities for detection of MCI on the t-MoCA were around 18 or 19. Additional research examining MCI following stroke using the t-MoCA and detailed neuropsychological testing found that a score cutoff of <19 for MCI on the t-MoCA was appropriate (Zietemann et al., 2017), and this is the cutoff used for this study. Permission to use this measure was obtained from the MoCA Clinic & Institute.

PHQ-9

The Patient Health Questionnaire – 9 (PHQ-9) is a publicly available depression scale that is short in length, but possesses comparable sensitivity and specificity to other longer measures, and evaluates presence and severity of depression symptoms (Kroenke et al., 2001). The PHQ-9 has been adapted from its original format as a primary care measure, to a telephone-administered measure that can be used in research (Pinto-Meza et al., 2005). The PHQ-9 provides data on depression severity, with higher scores indicating more severe depression, via numerically coding responses and adding them up to obtain a total score (Kroenke et al., 2001).

Brief Test of Adult Cognition by Telephone (BTACT)

The Brief Test of Adult Cognition by Telephone (BTACT) is an assessment of cognitive functioning that is designed to be conducted via the telephone, and incorporates multiple dimensions including episodic memory, working memory, reasoning, verbal fluency, and executive function (Lachman et al., 2014). The BTACT has strong psychometric properties and has been used to screen and track executive and memory function among liver transplant recipients (Ferman et al., 2019; Lachman et al., 2014). Permission for its use was obtained from one of the original authors.

Basel Assessment of Adherence to Immunosuppressive Medications (BAASIS©)

The BAASIS was used as a self-report assessment of medication adherence after permission was obtained from the University of Basel, Leuven-Basel Research Group. The BAASIS measure has demonstrated strong psychometric properties and asks questions on missing doses and time deviations greater than 2 hours within a 4-week recall period, in addition to questions on drug holidays, dose changes and medication discontinuation without a provider's consultation (Dobbels et al., 2010; Gustavsen et al., 2019).

Brief Illness Perceptions Questionnaire

The Brief Illness Perceptions Questionnaire (Brief IPQ) is designed to evaluate the illness representation dimensions, or the cognitive and emotional models that characterize individual interpretations of illness identity, consequences, timeline, control/cure and cause (Broadbent et al., 2006). The Brief IPQ uses a scale from 0 to 10 with higher scores indicating stronger perceptions on that particular dimension, except the causal dimension which allows for an open-ended response (Broadbent et al., 2015). This measure includes an item on illness coherence, or the extent to which an individual's representation contributes to a coherent understanding of their condition or illness (Moss-Morris et al., 2002). The Brief IPQ has been adapted and applied to transplant recipients (Broadbent et al., 2015; Massey et al., 2015), and this adapted version by Kung et al. (2012) was employed for this study. Permission to use this measure was obtained from Dr. Elizabeth Broadbent.

Data Analysis

Following data collection, the participant responses were entered into REDCap electronic data capture tools hosted at Mayo Clinic (Harris et al., 2019; Harris et al., 2009) and were then exported to IBM® SPSS® Statistics for Windows, Version 28.0. Demographic data were summarized using descriptive statistics. Point-biserial correlations and Pearson's correlations were used to evaluate the relationships between variables, while logistic regression was used to model predictors of adherence. The last six laboratory immunosuppression concentrations for each participant were used to determine tacrolimus trough variability via coefficient of variation calculations.

Results

Demographic data for the sample are summarized in Table 1. Of the 35 participants, 25 (71.4%) were males, and 10 (28.6%) were females. Most participants (n = 25, 71.4%) were white, married (n = 29, 82.9%), and well-educated, with over 77% (n = 27) having attended some college or more. The average age was 61 years, with a range of 30-75 years. The sample characteristics on gender and race closely mirror the transplant center's overall demographic data, in which 25.8% of total heart transplant recipients were female and 67.9% were white as of January, 2022 (OPTN, 2022). Of the 35 participants, 31.4% (n = 11) were classified as nonadherent, having reported either missing doses of their immunosuppression within the 4-week recall period of the BAASIS (n = 7), and/or taking medications over 2 hours before or after their usual dosing time (n = 8). Mild Cognitive Impairment was assessed using the t-MoCA, with scores of 19 or above considered normal. Table 2 describes the age characteristics of the participants that scored less than 19 (n = 8).

Self-Reported Medication Adherence

Table 3 describes the correlations of interest between select variables and self-reported medication adherence. Having no reported missed doses of immunosuppression was associated with higher immediate word recall (r_{pb} = .416, p = .013), fewer immediate word recall intrusions (r_{pb} = -.474, p = .004), and higher scores on t-MoCA delayed recall (r_{pb} = .355, p = .037). Among those participants who reported missing doses, the frequency with which they missed doses was positively associated with immediate word recall intrusions (r_{pb} = .904, p = .005) and higher reported trouble concentrating (r_{pb} = .884, p = .008). Participants who reported no missed doses had higher illness coherence scores (r_{pb} = .492, p = .003), measured by item 7 on the Brief IPQ (How well do you feel you understand your transplant?). Higher general overall health rating (r_{pb} = .351, p = .039) and higher overall satisfaction with health (r_{pb} = .378, p = .025) were also associated with reporting no missed doses.

Taking immunosuppression medication on time (e.g., within 2 hours of the usual dosing time) was associated with higher t-MoCA total scores (r_{pb} = .372, p = .028) and t-MoCA delayed recall scores (r_{pb} = .335, p = .049), and fewer delayed word recall intrusions (r_{pb} = -.364, p = .032). Those participants that took their medications on time also had lower PHQ-9 total scores, (r_{pb} = -.437, p = .009), lower rated frequency on PHQ-9 individual item 6 (feeling bad about yourself) (r_{pb} = -.585, p < 0.001), and individual item 7 (trouble concentrating) (r_{pb} = -.361, p = .033).

When participants were classified as adherent or nonadherent based on whether they missed doses or took medications over 2 hours outside of the usual dosing time, adherence was negatively associated with PHQ-9 total score (r_{pb} = -.338, p = .047), and positively associated with IPQ7 (r_{pb} = .519, p = .001). None of the participants reported that they had altered the prescribed amount of their immunosuppression or that they had stopped taking their medication all together without being advised by their provider to do this. Over 91% of participants (n = 32) rated the importance of their transplant medications on the Brief IPQ as a 10/10 indicating extreme importance.

Logistic regression was performed to identify possible predictors of medication adherence and the results of these analyses are presented in Table 4. The model using immediate word recall as a predictor of having no missed doses of immunosuppression was found to be the best fit of all the variables, correctly classifying 88.6% of the cases. For every 1 word increase on the immediate word recall portion of the BTACT, the odds of participants having no missed doses of immunosuppression increased 2.5 times. A logistic regression analysis was also performed to determine predictors of taking medications on time. The model that included PHQ-9 total score as a predictor was found to be a good fit, correctly classifying 82.9% of cases.

Tacrolimus Trough Variability

Of the 35 participants, 32 were on tacrolimus at the time of data collection and had enough laboratory data to calculate a tacrolimus coefficient of variation to indicate trough variability. Unsurprisingly, higher tacrolimus trough variability was negatively associated with adherence cases overall (r_{pb} = -.400, p = .023), and with taking immunosuppression medication on time (r = -.406, p = .021). Higher trough variability was negatively associated with backward digit span performance (r = -.383, p = .031) and trouble falling or staying asleep (r = -.402, p = .023). When trough variability was used to classify participants as nonadherent using tacrolimus trough variability of 30% or higher (Gustavsen et al., 2019), only 2 individuals demonstrated trough variability above this threshold, with 1 of those individuals having already been captured as nonadherent by the self-assessment.

There were no significant relationships between medication adherence (measured via self-report or tacrolimus trough variability) and age, time since transplant, education, marital status, or employment status. Having caregiver assistance with organizing medications and/or with remembering to take medications was not significantly associated with self-reported adherence or trough variability. All participants denied missing doses of medications related to an inability to afford their medication. Additionally, no significant relationships were identified with medication adherence and history of cardiac arrest, left ventricular assist device, mechanical circulatory support, or stroke.

Discussion

The purpose of this study was to explore relationships between cognitive function, illness perceptions, and medication adherence among heart transplant recipients. Additional demographic and clinical characteristics were also evaluated. In our sample, 22.9% of participants scored less than 19 on the t-MoCA, which may indicate MCI (Katz et al., 2021; Pendlebury et al., 2013). This number is higher than MCI prevalence in the general population (Petersen et al., 2018), particularly when examining the prevalence in the context of participant age; however, is lower than a previous study specific to heart transplant recipients, possibly due to differences in measurement or sample (Burker, Gude et al., 2017). T-MoCA total scores were not associated with age, education, or history of mechanical circulatory support, LVAD support, stroke or cardiac arrest. Thus, there may be a different pathophysiologic mechanism, for instance prolonged global hypoperfusion associated with heart failure, or impacts from comorbid conditions, which may be involved and warrant further investigation.

Immunosuppression medication nonadherence rates in our sample were consistent with the literature, confirming previous evidence that this population faces substantial challenges related to the implementation phase of medication adherence (Denhaerynck et al., 2018). To our knowledge, this is the first study that examined relationships between cognitive function and medication adherence among heart transplant recipients. The relationships between episodic memory, intrusions, and medication adherence represents a novel finding. Episodic memory, measured by word list recall, and inaccurate memory, measured by number of intrusions, may have important implications for the development of medication adherence interventions for this population. Word list recall intrusions occur when a word that was not on the word recall list is produced and have been shown to predict progression to MCI (Thomas et al., 2018), further supporting the possibility that this population is at high risk for developing cognitive impairment. Additionally, heart transplant recipients with MCI may be at risk for medication nonadherence. Incorporating screening for MCI into transplant practices should be considered so that factors contributing to the development of MCI can be addressed. The prevalence of MCI in this population should also be considered when developing interventions designed to support medication adherence.

When considering the relationship between illness perceptions and medication adherence, illness coherence was the only illness perception that was significantly associated with medication adherence. While illness coherence has been defined as an important variable in the literature and was associated with medication adherence in our study, associations with other illness perceptions that have been previously identified in mixed samples of solid organ transplant recipients were not found (Kung et al., 2012). This may be because of differences in perception among individuals that have received different organ transplant types, or because of limitations related to the sample.

In this sample, over 37% of the participants were categorized as having mild depression on the PHQ-9. We found associations between medication adherence, depression, and some specific items on the PHQ-9, indicating that depression, even when mild, was associated with adherence behavior. PHQ-9 total scores were not significantly associated with immediate word recall or immediate word recall intrusions in this sample but were associated with delayed word recall intrusions. These results indicate that depression is a psychiatric comorbidity that could influence cognitive function among this group.

This study has limitations. The cross-sectional design does not allow for causal inferences to be made. The use of a small convenience sample recruited from one transplant center via patient portal limits generalizability. While study sessions were conducted via telephone to reduce risk associated with in-person visits during the COVID-19 pandemic, challenges related to telephone administration of measures (e.g., difficulty hearing instructions) may have influenced the findings, although participants were asked to confirm their ability to hear instructions during the session. The telephone format of the study sessions also limited our ability to use cognitive measures that required in-person application. Additionally, the format of the measures did not allow for recruitment of non-English speakers.

Additional limitations include the use of self-report to capture medication adherence rates, although the adherence rates that were recorded did correspond to previous literature

(Denhaerynck et al., 2018). While we used a measure that has been widely used in the transplant literature, self-reporting on behavior represents a complex cognitive task that is highly context-dependent (Schwarz & Oyserman, 2001). The ability to accurately self-report medication adherence relies on memory, and given the associations between adherence, episodic memory, and intrusions identified in this sample, future studies should consider using electronic monitoring methods to further articulate this relationship. Tacrolimus trough variability was used as a secondary measure of adherence, and while the clinical utility of achieving stable plasma tacrolimus concentrations has been established (Gueta et al., 2018), we identified only one additional participant that met criteria for nonadherence based on this measurement.

The cross-sectional nature of the study design did not allow for longitudinal evaluation of medication adherence and cognitive test performance, limiting the ability to understand how these variables may change over time. Some participants that followed at the transplant center for post-transplant care but did not receive their transplantation surgery at the facility had limited records, potentially impacting the ability to draw conclusions based on characteristics of medical or surgical history.

Conclusion

Our findings indicate that cognitive impairment may be common among heart transplant recipients, and that cognitive test performance, specifically as it relates to episodic memory, inaccurate memory, and cognitive impairment, may be related to medication adherence in this population. Additionally, important relationships between illness coherence, depression, and medication adherence have also been identified. Future research should include longitudinal evaluation of cognitive test performance, depression, and medication adherence. Additionally, it will be important for future studies to consider the possible predictors of cognitive impairment that may exist in this population, and how this may relate to self-management behaviors and clinical outcomes. As interventions to promote medication adherence increasingly incorporate technology, researchers and developers should consider the unique human factors needs of this population, specifically as it relates to cognitive function.

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Table 1
Demographic Characteristics of the Sample

Demographic Characteristic	Mean (SD) or Number (Frequency)
Average Age	61 years (10.3)
Age Range	30 - 75 years
Gender	
Male	n = 25 (71.4%)
Female	n = 10 (28.6%)
Time Since Transplant	
Less than 1 year	n = 3 (8.6%)
Between 1 and 3 years	n = 9 (25.7%)
Between 3 and 5 years	n = 8 (22.9%)
Between 5 and 7 years	n = 7 (20%)
Over 7 years	n = 8 (22.9%)
Education	
High school graduate/GED	n = 3 (8.6%)
Vocational training	n = 5 (14.3%)
Some or in-progress college/Associate’s degree	n = 13 (37.1%)
Bachelor’s degree	n = 8 (22.9%)
Master’s degree or other post graduate training	n = 3 (8.6%)
Doctoral degree	n = 3 (8.6%)
Employment	
Employed full-time	n = 9 (25.7%)
Employed part-time	n = 5 (14.3%)
Student	n = 1 (2.9%)
Retired	n = 14 (40%)
On sick leave or disability	n = 5 (14.3%)
Unemployed or temporarily laid off	n = 1 (2.9%)
Race	
Asian	n = 1 (2.9%)
Black or African American	n = 2 (5.7%)
White	n = 25 (71.4%)
More than one race	n = 3 (8.6%)
Other	n = 4 (11.4%)
Hispanic	

Yes	n = 4 (11.4%)
No	n = 31 (88.6%)
Marital Status	
Single	n = 4 (11.4%)
Married	n = 29 (82.9%)
Divorced	n = 2 (5.7%)
T-MoCA Category	
Score < 19	n = 8 (22.9%)
Score ≥ 19	n = 27 (77.1%)
PHQ-9 Category	
No depression (score of 0)	n = 5 (14.3%)
Minimal depression (score of 1-4)	n = 17 (48.6%)
Mild depression (score of 5-9)	n = 13 (37.1%)
History of Left Ventricular Assist Device	
Yes	n = 10 (28.6%)
No	n = 25 (71.4%)
History of Documented Cardiac Arrest	
Yes	n = 6 (17.1%)
No	n = 29 (82.9%)
History of Documented Stroke	
Yes	n = 7 (20%)
No	n = 27 (80%)

Table 2

Age Characteristics of the Participants that Scored <19 on the t-MoCA

Age Range	Number of Participants that Scored <19 on the t-MoCA
41-50 years	n = 1
51-60 years	n = 3
61-70 years	n= 3
71-80 years	n = 1

Table 3

Correlations of Select Study Variables

Variables	1	2	3	4	5	6	7	8	9	10	11	12
1. BAASIS: no missed doses	-											
2. BAASIS: taking medications on time	**.41***	-										
3. Age	.05	.22	-									
4. Time since transplant	-.13	-.22	.16	-								
5. Education	-.09	-.07	.16	**.39***	-							
6. BTACT immediate word recall	**.42***	.18	-.28	-.31	-.07	-						
7. BTACT immediate word recall intrusions	**-.47****	-.20	-.06	.07	.15	-.40*	-					
8. BTACT delayed word recall intrusions	.28	**-.36***	.19	.06	.20	-.19	.20	-				
9. t-MoCA© delayed memory recall	**.36***	**.34***	.07	.19	.26	**.36***	-.14	-.01	-			
10. t-MoCA© total score	.32	**.37***	.01	.13	.15	**.41***	-.12	-.15	**.87****	-		
11. PHQ-9 total score	-.18	**-.44****	.05	-.09	.06	-.02	.30	**.36***	-.32	-.21	-	
12. Illness coherence	**.49****	.21	.20	-.21	-.15	.07	-.19	.19	.26	.07	-.18	-

Note. BAASIS© = Basel Assessment of Adherence to Immunosuppression Scale; BTACT = Brief Test of Adult Cognition by Telephone; t-MoCA© = Telephone Montreal Cognitive Assessment; PHQ-9=Patient Health Questionnaire 9.
*p<.05. **p<.01

Table 4

Logistic regression results predicting medication adherence

	B	***SE***	***Wald***	***df***	***P***	***Odds Ratio***	***95% CI for odds ratio***	
							Lower	***Upper***
No Missed Doses								
Constant	-4.13	2.19	3.56	1	0.06	.02		
Immediate Word Recall	0.93	0.40	5.46	1	0.02	2.54	1.16	5.55
Taking Meds on Time								
Constant	2.97	0.97	9.44	1	<0.01	19.52		
PHQ-9 Total Score	-0.42	1.80	5.42	1	0.02	0.66	0.46	0.94

Note. R^2 = 0.40 (Nagelkerke) for no missed doses; R^2 = 0.27 (Nagelkerke) for taking meds on time

APPENDIX D:

SITE APPROVAL AND THE UNIVERSITY OF ARIZONA INSTITUTIONAL REVIEW BOARD APPROVAL LETTER

MAYO CLINIC

Principal Investigator Notification:

From: Mayo Clinic IRB
To: Stacy Al-Saleh
CC: Stacy Al-Saleh

Re: IRB Application # 21-001508

Application Title: Executive Function, Cognitive Impairment, Illness Perceptions, and Medication Adherence Among Heart Transplant Recipients

Please note that all correspondence (modifications, continuing reviews, reportable events) related to this application must be submitted electronically in the IRBe system.

The following is an excerpt from the minutes of the Mayo Clinic Institutional Review Boards (IRB-C) meeting dated 4/30/2021:

DECISION: The Committee received the Deferral Response Form dated April 18, 2021, for the above referenced application. The investigator: 1) included a senior faculty from the heart transplant program; and 2) addressed the use of a statistician. The Committee determined that the concerns identified at the Committee meeting on March 26, 2021, were adequately addressed.

The Committee reviewed and approved the above referenced application and noted that all requirements for approval of research (45CFR46.111) were met. This approval is valid for one year unless during that time the IRB determines that it is appropriate to halt or suspend the study earlier. IRB approval will expire on April 29, 2022. The Committee approved the accrual of 60 adult subjects. The Committee approved the following site to conduct the study activities as specified in the application: Mayo Clinic in Arizona.

REVIEW: The Committee noted receipt of the protocol, Version 2 dated March 5, 2021.

CONTACT MATERIALS: The Committee approved the questionnaire and the telephone scripts as submitted.

CONSENT: The Committee approved the consent form (00) with minor edits. The final approved consent form will be provided under the Documents tab of the main study workspace in IRBe.

REMINDER: The Committee:

- Reminds the investigator to submit a continuing review report prior to the expiration date (reminder will be sent prior to expiration).

Attachments (if applicable):

name	version	dateCreated	dateModified
There are no items to display			

Vaszar, Laszlo T., M.D., Chair
Taylor Moen , Correspondent
Mayo Clinic Institutional Review Boards

IRB-C

THE UNIVERSITY OF ARIZONA
Research, Discovery & Innovation

Human Subjects Protection Program

1618 E. Helen St.
P.O.Box 245137
Tucson, AZ 85724-5137
Tel: (520) 626-6721
http://rgw.arizona.edu/compliance/home

Date:	June 17, 2021
Principal Investigator:	Stacy Anne Al-Saleh
Protocol Number:	2106868392
Protocol Title:	Executive Function, Cognitive Impairment, Illness Perceptions, and Medication Adherence Among Heart Transplant Recipients
Level of Review:	Administrative Review
Determination:	Approved
IRB of Record:	Mayo Clinic IRB
Investigator at Site:	Stacy Al-Saleh
IRB of Record Protocol Number:	21-001508

Documents Reviewed Concurrently:

Data Collection Tools: *Al-Saleh_Measures.docx*
HSPP Forms/Correspondence: *Advisor Confirmation Email.pdf*
HSPP Forms/Correspondence: *Al-Saleh_IRB Waiver.pdf*
HSPP Forms/Correspondence: *Al-Saleh IRB Application for Reliance June 1.pdf*
HSPP Forms/Correspondence: *Al-Saleh Personnel List.pdf*
HSPP Forms/Correspondence: *Confirmation for Scientific Review and Department Review.pdf*
Informed Consent/PHI Forms: *Al-Saleh_IRB Consent.pdf*
Protocol: *Al-Saleh_Mayo_IRB_Protocol_Revised_May27.docx*
Recruitment Material: *Al-Saleh_Recruitment_portalscript_March24.docx*
Recruitment Material: *Al-Saleh_Recruitment_SupportGroup_March24.docx*
Recruitment Material: *Electronic Consent Process and Phone Call Revised March 23.docx*
Recruitment Material: *Email Consent Script.pdf*
Regulatory Documentation: *2106868392 Al-Saleh UA Cede to Mayo_SMART IRB LOA_UA signed 6.4.pdf*
Regulatory Documentation: *Al-Saleh_IRB approval.pdf*

Regulatory Determinations/Comments:

- Institution Designated IRB of Record: When an institution is designated IRB of record, the UA IRB will not review the project. The University of Arizona agrees that it will rely on the review, approval, and continuing oversight of the institution's IRB pursuant to the terms of the Institutional Review Board Authorization Agreement.
- Waiver of PHI Authorization (45 CFR 164.512(i)(2)(ii)): As documented in the file, the use or disclosure of protected health information involves no more than minimal risk to the individuals ; the research could not practicably be conducted without the alteration or waiver ;the research could not practicably be conducted without access to and use of the protected health information ; there is an adequate plan to protect the identifiers from improper use and disclosure ; there is an adequate plan

to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law ; and there are adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart.

- The University of Arizona maintains a Federalwide Assurance with the Office for Human Research Protections (FWA #00004218).
- All documents referenced in this submission have been reviewed and are filed with the HSPP. The Principal Investigator should notify the IRB immediately of any proposed changes that affect the LOCAL protocol and report any LOCAL unanticipated problems involving risks to participants or others. Please refer to Guidance's *Investigators Responsibility after IRB Approval* and *Reporting Local Information*.
- All research procedures should be conducted according to the approved protocol and the policies and guidance of the IRB of record.