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Long-term Use of Beta-blocker Medication in Pediatric Long QT Syndrome Patients: Neuropsychological Profiles

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LONG-TERM USE OF BETA-BLOCKER MEDICATION IN PEDIATRIC LONG QT SYNDROME PATIENTS: NEUROPSYCHOLOGICAL PROFILES

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Dissertation Approval

This is to certify that the thesis presented to us by Kara Rudisill on the 7 day of January, 2019, in partial fulfillment of the requirements for the degree of Doctor of Psychology, has been examined and is acceptable in both scholarship and literary quality.

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Dedication

This project is dedicated to my parents, John and Joy Rudisill. You two will forever be the original loves and light of my life.

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Abstract

Long QT syndrome (LQTS) is a heart rhythm disorder characterized by a disruption of the heart's electrical activity that may cause accelerated and uncontrolled heartbeats referred to as ventricular fibrillation. LQTS is primarily treated with beta-blocker medications, which reduce the risk of experiencing an arrhythmia through regulating the heart rate. However, the potential neuropsychological side-effects associated with the use of beta-blocker medication may impact the executive functioning skills, mental health, and behavior of the affected pediatric population at home. As a result, a child's academic performance and emotional regulation etiology may be misunderstood by his or her parents, caregivers, and teachers. The present study used an exploratory research design to further understand and conceptualize neurocognitive profiles of children diagnosed with LQTS and concurrently taking beta-blocker medications. Three participants were administered tailored test batteries with commonly used measures that assess general intellectual functioning, academic achievement, memory and new learning, fine motor and dexterity, and executive functioning skills. Additionally, the participants were administered self-report measures that assess symptoms associated with depression and anxiety, as well as self and parental perceptions of disease impact on quality of life. Overall, the participants demonstrated several inefficiencies within their executive functioning skills and basic sustained attention that had been were documented in their past educational histories, as well as in their performances on measures within the current study.

Table of Contents

List of Tables vii

Chapter 1: Introduction 1

Statement of the Problem 3

Purpose of the Study 3

Chapter 2: Literature Review 5

Long QT Syndrome (LQTS) 5

Cognitive side-effects of other commonly prescribed medications 8

Neurological side-effects associated with long-term medication use 9

Beta-Blockers 10

Cognitive side-effects of beta-blocker medication 18

Differentiating side-effects of various beta-blockers 20

Anxiety and Quality of Life of Children Diagnosed with LQTS 21

Impact of living with a chronic illness 22

Quality of life and psychological adjustment 23

Chapter 3: Research Question and Hypotheses 23

Research Question 23

Hypotheses 23

Chapter 4: Method 24

Design 24

Participants and Setting 24

Procedure 24

Evaluation Day 27

Data Collection 29

Chapter 5: Results 30

Background: Participant M31F/ “Sam” 30

Evaluation Results: Participant M31F/ ”Sam” 31

Background: Participant M03M/ “Tim” 33

Evaluation Results: Participant M03M/ “Tim” 33

Background: Participant J06F/ “Jade” 35
Evaluation Results: Participant J06F/ “Jade” 36
Chapter 6: Discussion 39
Intellectual Functioning Differences 39
Academic Achievement Differences 41
Memory Differences 42
Executive Functioning Differences 43
Fine-Motor Skills Differences 44
Mental Health Differences 45
Quality-of-Life Differences 46
Implications 48
Limitations 49
Future Directions 51
References 53
Appendix: Study Eligibility Questionnaire 71

List of Tables

Table 1. Summary of Demographic and LQTS Information......................................26
Table 2. Intellectual Functioning: Wechsler Intelligence Scale for Children: Fifth Edition (WISC-V)..41
Table 3. Academic Achievement Screener: Wechsler Individual Achievement Test: Third Edition (WIAT-III) 42
Table 4. Memory Tasks: Wide Range Assessment of Memory and Learning: Second Edition (WRAML2)...43
Table 5. Executive Functioning Tasks: Delis-Kaplan Executive Function System (D-KEFS) 44
Table 6. Fine-Motor Tasks: Grooved Pegboard Test (GPT) 45
Table 7. Behavioral Questionnaires: Children's Depression Inventory: Second Edition (CDI-2) 46
Table 8. Behavioral Questionnaires: Screen for Child Anxiety Related Disorders (SCARED) CHILD Version...46
Table 9. Behavioral Questionnaires: Pediatric Cardiac Quality of Life Inventory (PCQLI) 48

Chapter 1: Introduction

Congenital heart defects (CHDs) are one of the most commonly observed birth defects and leading causes of birth defect-associated infant illness and death (Oster et al., 2013). The incidence rate of congenital heart defects (CHDs) is approximated at 4/1,000 to 50/1,000 live births per year in the United States (Hoffman & Kaplan, 2002). Long QT syndrome (LQTS) is a specific cardiac condition characterized by quick, sporadic heartbeats that may cause a loss of consciousness and potentially seizures (Giudicessi & Ackerman, 2013). LQTS is most commonly treated with beta-adrenergic blocking agents (beta-blockers; Al-Khatib et al., 2018). Though all beta-blockers are categorized under one class of hypertensive medication, each member within the class may demonstrate major pharmacologic differences and physiologic side-effects (Duan, Ng, Chen, Spencer, & Lee, 2018). Some of the most commonly prescribed beta-blockers include atenolol, propranolol, and metroprolol (Ripley & Saseen, 2014). Beta-blockers effectively mitigate the hormone epinephrine (i.e., adrenaline) and improve blood flow throughout the body by slowing heart rate and force (Frishman & Saunders, 2011). Beta-blockers have proved to be a crucial treatment option for those diagnosed with congenital heart disease, resulting in a decreased emphasis on studying central nervous system (CNS) side-effects (Lawley, Siegfried, & Todd, 2009).

The use of beta-blocker medication may affect various functions of the CNS, including behavioral functions, such as mood disturbances, disorganized thought processes, and concentration (Koella, 1985; Westerlund, 1985). These disturbances may manifest through mental fatigue, sleep disturbances, nightmares, hallucinations, and symptoms of confusion (Dahlof & Dimenas, 1990). Additionally, beta-blocker use has been associated with distinct personality changes, including mood swings and symptoms of depression (Westerlund, 1985).

Further, research has detailed that patients taking propranolol for cardiac arrhythmias experienced suicidal thoughts (Waal, 1967), in addition to patients post myocardial infarction experiencing an increase in depressive symptoms during the first year of beta-blocker use (van Melle et al., 2006). These neurocognitive symptoms are often assessed through the use of neuropsychological measures (Parsons, Carlew, Magtoto, & Stonecipher, 2017). Neuropsychological measures are used to assess specific functionality of brain activity in such areas as memory, attention, executive functioning, and personality (Harvey, 2012). Neuropsychological assessment relies upon the concept of ecological validity, which is defined as a “real world” connection between test scores and inefficiencies in activities of daily living (Lange et al., 2014). This concept is also defined in the literature as brain-behavior relationships. Beta-blockers may contribute to various neuropsychological effects through their lipid solubility in the CNS, which determines the penetration levels of the medication (Stein & Strickland, 1998). Specifically, a greater solubility of beta-blocker medication is equal to a greater penetration of medication and potentially more neuropsychological effects (Kearns et al., 2003). Therefore, experienced side-effects may vary from patient to patient. In extreme cases, medication toxicity may contribute to neurodevelopmental side-effects in the developing brains of children, most profoundly observed in their executive functioning abilities (Farlow & Hake, 1998). In the pediatric population, measurable neuropsychological differences are often discovered through academic achievement and intelligence testing (Dennis et al., 2009). Children’s classroom behaviors and academic achievements may exhibit deficits and differences compared to the behaviors and achievements of their same-aged peers. Therefore, individual scholastic achievement may be compromised as a result of beta-blocker use and should be more thoroughly investigated.

Statement of the Problem

The neuropsychological side-effects associated with the use of beta-blocker medication may impact the pediatric population's mental health, executive functioning skills, and behavior at home (Lawley et al., 2009). As a result, the etiology of individuals' below-grade-level academic performances and emotional dysregulations may be misunderstood by their parents, caregivers, and teachers. However, clinical literature regarding the potential associated side-effects of beta-blocker medication within cognitive domains is limited and have often yielded mixed results regarding an association (Burkauskas et al., 2015). Further, most studies fail to assess a variety of cognitive domains in a comprehensive manner and instead evaluate global cognitive abilities and functioning. Therefore, further investigation is required to more completely understand the potential side-effects of beta-blocker medication within specific cognitive domains.

Purpose of the Study

The purpose of the current study was to provide exploratory, phenomenological case studies of pediatric patients diagnosed with LQTS who had taken beta-blockers for a minimum of 1 to 2 years. The current study recognizes that past research regarding CNS side-effects associated with beta-blocker medication is limited and has been met with mixed conclusions. Thus, the current study seeks to further understand neuropsychological profiles of children diagnosed with LQTS and taking beta-blockers on a long-term basis to potentially lay groundwork for a more comprehensive, larger scale study, if indicated. The current study provides detailed, neuropsychological case study profiles of pediatric patients diagnosed with LQTS and taking beta-blocker medication on a long-term basis. Neuropsychological test batteries were administered to children within the age range of 8 to 16 years. It was hypothesized that long-term beta-blocker use may impact participants’ scores on measures sensitive to neuropsychological functioning in several specific domains.

Chapter 2: Literature Review

This literature review defines various constructs related to the conceptualization of neuropsychological side-effects associated with long-term use of a medication. The side-effects of other commonly prescribed medications are discussed for comparison and reference. The review includes a discussion of the definitions of neuropsychological domains, such as executive functioning, memory, attention, visual-motor abilities, and general intelligence in the pediatric population. Additionally, mental health domains, such as anxiety, depression, and quality of life, are defined, and examples of these affected domains in the pediatric population are provided. One should note that a significant amount of the following research cited is more than 10 years old because of limited research within the area.

Long QT Syndrome (LQTS)

LQTS is a congenital heart condition that is characterized by delayed ventricular repolarization manifest on the electrocardiogram as QT prolongation (Goldenberg, Zareba, & Moss, 2008). LQTS may also be acquired through drug therapy, hypokalemia (i.e., low potassium), or hypomagnesemia (i.e., low magnesium; Camm, Malik, & Yap, 2008). The variations of LQTS include the Romano-Ward and Lange-Nielsen forms of the syndrome. The Romano-Ward form of LQTS is characterized by autosomal-dominant inheritance without a history of familial deafness, while the Lange-Nielsen form of LQTS is associated with deafness (Nakano & Shimizu, 2016).

Diagnosing LQTS has proved to be a difficult task among healthcare professionals, as LQTS has presented in patients with an unremarkable family history (Ebrahim, Williams, Shepard, & Perry, 2017). Additionally, the QT interval varies greatly from person to person, making the standard presentation of LQTS difficult to discern. Medical professionals are often able to determine a diagnosis by ordering a genetic test that analyzes DNA markers but have also found that the genetic tests are not always infallible (Lustig & Lettenga, 2009). Testing may reveal genetic polymorphisms and not disease-causing mutations that affect the function of the gene (Sharma et al., 2004). Specific gene mutations, such as P448R-KVLQT1, have mistakenly been identified in the past as disease-causing mutations, and individuals who had this “bad gene” were subsequently thought to have LQTS (Kapplinger et al., 2009). However, the P448R gene mutation does not affect the working of the LQTS ion channel. Labs often do not complete patch-clamp analysis to determine whether a mutation has caused the disease and only compares an alleged mutation with matched controls and make their determinations as a result. Additionally, a negative result from a gene test does not automatically mean that the individual does not have LQTS, as only 64 to75% of patients with LQTS ultimately have their gene identified (Moric-Janiszewska et al., 2007). Therefore, 25 to 36% of individuals with LQTS may remain undiagnosed as long as they are asymptomatic. LQTS is most commonly inherited as an autosomal-dominant trait, meaning that half of an affected parent’s offspring will also inherit the LQTS gene mutation. The current criterion for diagnosing LQTS includes gathering data, such as the length of the QT interval, episodic syncope, and family history, from an individual suspected of having LQTS to calculate a diagnostic score (Hayashi et al., 2016). These examples of various domains are included in calculating the diagnostic score and are assigned various points in order to determine the individual’s probability of having LQTS. For example, a score of 4 or greater equates to an individual's high probability of having LQTS. Taken together, as diagnosing LQTS is often a complicated process, medical professionals must carefully consider an individual’s symptoms along with results from an electrocardiogram.

The specific course of medical treatment for LQTS depends on the type of LQTS diagnosed in the individual. The literature supports several medical treatments for LQTS, including beta-blocker therapy, internal cardioverter-defibrillators, pacemakers, and restriction of competitive sports and recreational activities. Within these options, the initial treatment for LQTS is beta-blocker medication. Beta-blockers slow the heart rate while decreasing L-type calcium current activity and preventing catecholamine from binding to beta-adrenergic receptors (Kubon et al., 2011; Viitasalo et al., 2006). Although beta-blockers are an effective and widely prescribed medication to treat LQTS, both physical and cognitive side-effects have been reported (Dimsdale & Newton, 1992). The physical side-effects of beta-blocker medications include syncope (i.e., temporary loss of consciousness and posture) and an increased risk for sudden arrhythmic cardiac death (Moss et al., 2000). However, clinical literature regarding the potential associated side-effects of beta-blocker medication within cognitive domains is limited and have often yielded mixed results regarding an association (Burkauskas et al., 2015). A review of the literature related to the cognitive side-effects of beta-blockers from 1970 to 1988 was inconsistent, as many studies within the articles used small sample sizes (i.e., < 20 subjects) and failed to include any consistent neuropsychological test battery, making difficult the detection of dependable deficits. Specifically, while the literature contains demonstrated evidence that beta-blockers adversely affect perceptual motor functioning, other case studies suggested that they improve complex task performance. In addition, while the literature has demonstrated mild sedation and fatigue associated with beta-blocker use, reports have correlated those effects with beta-blockers with higher lipophilic agents. Lastly, symptoms related to depression have been associated with beta-blocker use, but only in case studies. Overall, literature involving the cognitive side-effects associated with beta-blocker use are not as well documented and researched as are other side-effects of other commonly prescribed medications.

Cognitive side-effects of other commonly prescribed medications. The literature regarding the cognitive side-effects of other commonly prescribed medications, such as benzodiazepines and dopaminergic medications, are more widely researched and understood than those of beta-blockers (Barker, Greenwood, Jackson, & Crowe, 2004; Cools, Van den Bercken, Horstink, Van Spaendonck, & Berger., 1984). The cognitive side-effects of both benzodiazepines and dopaminergic medications are similar to those of beta-blockers, asserting the need for further research.

Neurologic side-effects associated with long-term medication use. Many prescription medications of different classes have been studied in the past regarding their long-term effects on the CNS. Specifically, long-term use of benzodiazepines, one of the most commonly prescribed medications for depression, panic disorder, and anxiety, is cautioned against due to the reported associated psychological side-effects (Chen & Lader, 1990). In a recent meta-analysis, long-term benzodiazepine use was correlated with several affected neuropsychological domains when compared to controls (Barker et al., 2004). In the 13 studies reviewed, long-term benzodiazepine use was found to be related to nonverbal memory impairment and both verbal learning and verbal memory. Long-term benzodiazepine use was found to be correlated also with significant impairments in attention, concentration, and visual-spatial abilities (Birzele, 1992; Tata, Rollings, Collins, Pickering, & Jacobson, 1994).

Dopaminergic medications are another commonly prescribed prescription medication that has documented cognitive side-effects. Dopaminergic medications are targeted to treat the mesocorticolimbic dopamine system, an area of the brain that has been established to contribute to cognitive processes, such as working memory (Brozoski, Brozoski, Brown, Goldman, & Rosvold, 1979; Castner & Goldman-Rakic, 1992; Goldman-Rakic & Williams, 2000; Hollerman, Schultz, & Tremblay, 2000). One of the most recognized diseases associated with dopaminergic medications is Parkinson's disease (Cools, Barker, Sahakian, & Robbins, 2001). Patients diagnosed with Parkinson's disease are placed on medications, such as L-dopa, to address subtle cognitive impairments (Taylor, Lang, & Saint-Cyr, 1986; Owen et al., 1995). Further, Taylor, Lang, & Saint-Cyr (1986) detailed that the cognitive impairments observed in patients with Parkinson's disease are similar to those observed in patients with frontal-lobe damage. These cognitive impairments may include strategic planning, attentional set-shifting, and spatial working memory (Flowers & Robertson, 1985; Milner, 1964). However, deficits in strategic planning seen in patients with Parkinson's disease must be interpreted with caution, as age and IQ pre-diagnosis may also play a role in the overall neuropsychological profile of the patient (Canavan et al., 1989). In addition to cognitive dysfunction, research has also found that dopaminergic medications may enhance task demands in patients with Parkinson's disease (Cools et al., 2001). Taken together, long-term use of a medication must be monitored closely from research and clinical perspectives, as long-term use may present both cognitive enhancements and deficits in patients.

Beta-Blockers

Beta-blockers have been the first line of therapy in individuals diagnosed with LQTS since patients were successfully treated by a group of New York cardiologists in the mid-1970s (Goldenberg et al., 2008). The first study regarding the safety and efficacy of beta-blocker medication in treating patients with LQTS was conducted in a randomized, double-blind, placebo-controlled trial in 1999 (Moss et al., 2000). Patients with LQTS were recruited through the International LQTS Registry to determine the risk factors for syncope, aborted cardiac arrest, and death during the prescribed beta-blocker course of therapy. Beta-blocker medication was found to be associated with significantly reduced cardiac events in patients with LQTS; however, syncope, aborted cardiac arrest, and LQTS-related deaths continued to occur in patients while on beta-blocker medication. The risk factors for cardiac events during prescribed beta-blocker medication therapy include the age that beta-blocker therapy began (i.e., <5, 5-9, >=10 years) and the symptoms before beta-blocker therapy, including syncope and aborted cardiac arrest. These physical risk factors are well documented in the literature, with the cognitive side-effects often detailed in phenomenological case studies that target such domains as memory, psychomotor slowing, and mental health side-effects.

Cognitive side-effects of beta-blocker medication. The most commonly reported side-effects associated with beta-blockers are significant for neurocognitive symptomology including fatigue, lethargy, depression, sleeping difficulties (e.g., nightmares, insomnia, hypersomnia, etc.), in addition to memory (Cahill, McGaugh, Prins, & Weber, 1994; Barron et al., 2013). These domains will be more completely delineated below.

Memory. Working memory is defined as the brain’s ability to store volumes of information and use that information over periods of time (Baddeley & Hitch, 1974; Just & Carpenter, 1992). Working memory is best conceptualized as a collaborative process involving various neural functions, with the primary component being the central executive (Alloway, Gathercole, Willis, & Adams, 2004). Baddeley and Hitch (1974) proposed a working-memory system that involved the central executive as being responsible for reasoning, decision making, and coordinating tertiary “slave systems” (Logie, 2014). These slave systems include the visual-spatial sketch-pad (VSSP) and the articulatory loop. The VSSP has been regarded as responsible for the temporary storage and manipulation of visual-spatial information, while the articulatory loop (has since been renamed the phonological loop) is responsible for the storage and manipulation of verbal material (Logie, 2014). Lichter, Richardson, and Wyke (1986) sought to further understand side-effects associated with commonly prescribed beta-blockers, such as atenolol and enalapril, on the memories of patients in treatment for essential hypertension. The authors used a randomized single-blind study comparing patients taking atenolol versus enalapril, an enzyme inhibitor. In the 13 patients taking atenolol, a mild yet stable deficit involving memory functioning was observed. The mild memory deficits in the atenolol group were found to be in various aspects of memory functioning, including acquisition and short- and long-term recall. Lichter and Wyke (1986) compared the findings to another study that found a verbal-memory impairment in subjects taking methyldopa or propranolol beta-blockers (Solomon et al., 1983).

Solomon et al. (1983) found specific memory impairments, such as verbal memory, in patients taking two different blood pressure medications, methyldopa and propranolol hydrochloride. However, conflicting research has asserted that hypertension may be related to memory loss, as constricted blood flow to the hippocampus may cause memory impairments (Jennings et al., 2005). Thus, memory impairment related to hypertension is usually attributed to chronic hypertension cases that went untreated, and not always attributable to beta-blocker use. However, atenolol, a beta-blocker characterized by a low-lipid solubility, is not as well distributed in the brain as more highly lipid-soluble beta-blockers, such as propranolol (Day, Hemsworth, & Street., 1977). Therefore, the mild memory impairments seen in patients taking atenolol have suggested that low-lipid solubility is not as effective in protection against CNS side-effects of the drug and may be attributable to memory impairments in some individuals. The implication that possible memory impairments may result from breakdown of beta-blockers in the CNS is significant, as animal studies have found beta-blockers to be most concentrated in the hippocampus, the part of the human brain most closely associated with memory (Garvey & Ram, 1975).

Psychomotor slowing. Psychomotor slowing is defined as a sedative state, characterized by slowed movement and thought processes (Tryon, 2013). Psychomotor slowing is gradually observed in an individual's physical mobility, daily activities of living, and formal neuropsychological tests sensitive to speed (Sacktor et al., 1996). Psychomotor slowing is a common side-effect observed in individuals diagnosed with mood disorders, dementia, and Parkinson's disease (. However, psychomotor slowing may be associated with adverse side-effects of prescription medication use, such as benzodiazepines (Gudex, 1991) and beta-blockers (Selnes et al., 1991; Van Gorp, Miller, Satz, &Visscher, 1989). Research has demonstrated that reports of sedation and psychomotor slowing have been associated with beta-blocker use (Ades, Gunter, Meacham, Handy, & LeWinter, 1988). Additionally, individuals taking beta-blockers may be found to have significantly lower processing speeds as compared to controls (Hudak, Edwards, Athilingam, & McEvoy, 2013).

Beta-blocker medication affects neuropsychological functioning primarily through the peripheral nervous system (Noyes, 1982). Additionally, changes in blood pressure may affect neuropsychological functioning in patients, as biofeedback management of blood pressure has demonstrated improvements in cognitive functioning (Goldman, Kleinman, Snow, Bidus, & Korol, 1975). Beta-blockers may cross-bind with serotonin receptors and subsequently mimic an antagonist, thereby disturbing certain behavioral activities that are organized by networks in the brain (Koella, 1985). Thus, since emotional states characterized by stress and anxiety are regulated in the amygdaloid nucleus, the suppression of transmission activity by beta-blockers may impact overall cognitive functioning by blunting typically intensely experienced emotions (Margules, 1971). Therefore, beta-blockers may provide anxiolytic side-effects similar to those of commonly prescribed antianxiety agents (Tyrer, 1980).

Prior studies involving beta-blockers are characterized by small sample sizes and variability in design methodology (Stein & Strickland, 1998). Additionally, isolating and attributing any specific component of the treatment process as the sole cause of cognitive dysfunction in patients diagnosed with cardiac conditions is difficult. Specifically, psychomotor slowing may be associated with the anxiolytic effects of beta-blockers, which may benefit individuals that experience anxiety, but could elicit lethargy in others (Muldoon, Manuck, Shapiro, & Waldstein, 1991). Mild levels of psychomotor slowing may provide relief from anxiety, but greater levels may cause patients to enter mildly dreamlike states that may impact their daily functioning. Side-effects associated with the CNS are reported at approximately 10%, with approximately 5% of patients discontinuing use of beta-blockers because of adverse effects (Stewart, 1990). Thus, health professionals must be aware of the possible negative side-effects associated with beta-blocker use, especially in individuals who may be diagnosed with a mental health condition. Educational personnel also benefit from understanding the possible cognitive side-effects of beta-blockers in children and adolescents who may be below grade level academically. Taken together, children and adolescents taking beta-blockers on a long-term basis may demonstrate lower than expected skills and inefficiencies within specific domains of their executive functioning that may impact their academic performance.

Executive functioning skills in the classroom. Executive functioning inefficiencies in the pediatric population are often first noticed by parents, teachers, and other educational instructors in the classroom or after-school activities (Bull, Espy, & Wiebe, 2008). Many children and adolescents may have average to above-average intelligence but still have difficulties in sustaining attention and completing simple tasks throughout the day (Dennis et al., 2009; Dawson & Guare, 2009a). These difficulties are tied to inefficiencies in executive functioning skills, including preparation and planning, self-initiating work, emotion regulation, and adaptability (Culbertson & Zillmer, 1998). These skills do not develop identically and are often formed in the first 2 decades of life. Children with executive functioning inefficiencies may find completing simple chores, such as cleaning their rooms, much more challenging to accomplish than the average child. Specifically, tidying up a bedroom involves efficient executive functioning skills (e.g., planning the area of the room to clean first, choosing cleaning supplies, and estimating how long the entire process may take). Additionally, children with executive functioning inefficiencies may feel increased pressure and stress to complete tasks, as many parents and caretakers may not understand how to alter their instructions to best fit the way their children process information. Thus, the development of stable and efficient executive functioning skills is crucial to an individual's capacity to acquire skills and knowledge over his or her lifespan (Geary, Hoard, Byrd-Craven, Nugent, & Numtee, 2007).

Dawson and Guare's (2009b) model of conceptualizing executive functioning skills in children and adolescents considers both strengths and weaknesses within their *discrete skills*, including response inhibition, working memory, and emotional control. Executive functioning skills follow a developmental framework, with most children reaching a critical period of development between 7 and 9 years of age (Anderson, 2002). Such skills as cognitive flexibility, goal setting, and information processing are typically intact by the time children reach 12 years of age. In the education realm, lower-elementary-school teachers have reported that task initiation and sustained attention were the most difficult tasks for students to master (Dawson & Guare, 2009b). Task initiation is defined as a child's ability to begin a task or project on his or her own without prompting or delay, and sustained attention is a child's ability to maintain focus on a task for a set amount of time, despite possible distractions. Middle-school teachers have reported that time management, organization, and planning/prioritization were most difficult for students, and interestingly, selected response inhibition was the most concerning skill deficit reported. Response inhibition is defined as the child's ability to think before acting and to be able to restrict verbalization of his or her first thought. Taken together, these executive functioning skills contribute to a child's behavior and temperament in the classroom and at home. A child's inability to inhibit automatic responses, self-plan tasks, and sustain attention may adversely impact academic success, as well as positive social relationships (Blair, 2002).

Crystallized intelligence. Executive functioning skills are strong predictors of long-term achievement outcomes in children and adolescents (Bull et al., 2008). Specifically, children's academic performance in mathematics and reading depends on basic learned skills that are necessary to complete complex tasks. These general developed abilities include letter recognition, spelling, phonemic awareness (i.e., ability to recognize small units of sound that combine to produce words), and number recognition (Geary, Hamson, & Hoard 2000; Geary, Hoard, & Hamson, 1999). These skills combine to produce *crystallized intelligence* (Gathercole, Pickering, Knight, & Stegmann, 2004). Crystallized intelligence relies upon life experiences and skills to engage in higher level cognitive processes, such as the academic demands found in the classroom and the completion of chores and responsibilities at home. For example, response inhibition was found to be related to a range of academic ability measures, such as mathematics, phonemic awareness, and letter knowledge (Blair & Razza, 2007).

Response inhibition and phonological skills. Children with poor response inhibition have demonstrated lower scores in reading comprehension and mathematics and have also demonstrated difficulty recalling task instructions as compared to their peers (De Beni, Palladino, Pazzaglia, & Cornoldi, 1998; Pasolunghi, Cornoldi, & De Liberto, 1999). Additionally, longitudinal studies have demonstrated that children from ages 6 to 11 years have demonstrated difficulties in math computation skills, as well as phonological decoding (Mazzocco & Kover, 2007). Phonological decoding measures the ability to sound out small sounds (i.e., phonemes) and place them together to create whole words and is regarded as one of the most important skills that contribute to early overall reading abilities (Goswami & Ziegler, 2005; Share, 1995). Phonological decoding teaches children to understand these various "phonological codes," in an effort to create a foundation of language skills that will transfer to creating new words in the future (Nation & Snowling, 1998). Language deficits in children and adolescents may affect reading, speech, and socialization (Snowling, Bishop, & Stothard, 2000). Therefore, health professionals working with children and adolescents are often able to connect these skill deficits to an underlying executive functioning issue (Dick et al., 2001). Children taking a long-term medication that has potential CNS side-effects must be monitored for these possible deficits, which must be addressed in treatment (Bull & Scerif, 2001).

Visual-spatial skills. In addition to phonemic-awareness skills, visual-spatial skills and visual-spatial working memory in children and adolescents have been found to be related to early mathematics abilities (Geary, 1993). Specifically, deficits in visual-spatial skills may impact the abilities of children and adolescents to reverse, estimate, and execute mental math (Dehaene & Cohen, 1997). Also, children may exhibit difficulties in solving subtraction problems that require borrowing, in aligning column digits properly, and in attending to operational signs. Children and adolescents with deficits in their visual-spatial skills and working memory may achieve lower scores (as compared to same-aged peers) on mathematics tests of achievement and exhibit difficulties in completing simple math problems in an everyday situation (Bull et al., 2008). Taken together, research has correlated visual-spatial skills and understanding of spatial relations with skill development in mathematics (Dark & Benbow, 1990).

Mental health. Mental health is one of the most heavily researched domains related to the associated side-effects of various prescription medications (Stein, Miller, & Trestman, 1991). Beta-blockers cross the blood-brain barrier, which reduces the efficient flow of behavioral-systems information and causing a depressive effect in the CNS (Drayer, 1987). Timolol is a commonly prescribed beta-blocker used to treat glaucoma (Zimmerman & Kaufman, 1977). Timolol has reportedly been associated with changes in energy, including fatigue, drowsiness, and muscle weakness (Steiner, Friedhoff, Wilson, Wecker, & Santo, 1990). Timolol's other side-effects associated with emotional stability include erratic mood swings, lethargy, and heightened anxiety (Stewart, 1990). Timolol has been linked to symptoms of depression and sexual dysfunction in users (Duch et al., 1992). Past research regarding the differences of the associated side-effects of a nonselective beta-blocker (i.e., timolol) and a selective beta-blocker (i.e., betaxolol) found that patients using timolol experienced greater side-effects related to depression, as measured by the Beck Depression Inventory and the Zung-Conde scales (Duch et al., 1992). Taken together, the results suggested that timolol may exhibit greater depressive side-effects as compared to betaxolol.

Each beta-blocker type within the medication class does not demonstrate the same side-effects and should be monitored closely (Podrid, 2014). Research has demonstrated that the demographic reporting the most mental health side-effects associated with beta-blocker use are generally in the adult age range, with children and adolescents reporting fewer than adults (Forte & Weber, 1987). However, the research regarding in-depth neuropsychological profiles of children and adolescents taking beta-blocker medication and whether they experience side-effects as they age is limited.

Differentiating side-effects of various beta-blockers. Approximately 20 beta-blockers are commonly prescribed in the United States (Wiysonge et al., 2017). Medical professionals tailor beta-blocker prescriptions based on the specific condition of their patients. For example, some beta-blockers block all B-adrenergic receptors, and others selectively block only B-adrenergic receptors that are in targeted areas, such as the heart and kidneys. Kostis and Rosen (1987) found that the most frequently reported side-effects related to the use of beta-blockers included fatigue and lethargy, the primary reasons for discontinued use. Fatigue and lethargy are physical symptoms that are often associated with depression (Larkin & Martin, 2017). In a case study conducted by Petrie, Maffucci, and Woosley (1982), three women aged 21, 33, and 42 years reported depressive symptoms after use of propranolol. The women reported depressive side-effects beginning at the initial dose of propranolol and remitting once discontinued. Owing to these results, the authors warned that the use of propranolol in patients with a history of depressive symptoms may cause them to experience exacerbated depressive symptoms. Additionally, beta-blocker users have reported experiencing night terrors, vivid dreams, and insomnia, which may contribute to daytime drowsiness in patients (Kirk & Cove-Smith, 1983; Zacharias, 1975). Thus, reported mental health symptoms associated with beta-blocker use must be interpreted on a case-by-case basis. Specifically, healthcare professionals may have difficulty differentiating between clinical depression and a pseudo depressive state, including symptoms of muscle fatigue, weakness, and psychomotor slowing in these patients, because of the various areas that beta-blockers target in the human body (Paykel, Fleminger, & Watson, 1982).

Physically, lipophilic beta-blockers cross the blood-brain barrier, associating them more commonly than hydrophilic beta-blockers with CNS side-effects. Propranolol, a lipophilic beta-blocker, has been associated with depression in small case studies and reports (Huffman & Stern, 2007). Specifically, in a study conducted by Thiessen, Wallace, Blackburn, Wilson, and Bergman (1990), propranolol was found to be more associated than other nonlipophilic and hydrophilic beta-blockers with participants seeking antidepressant prescriptions. Additionally, in a study that compared the quality of life in patients taking various kinds of beta-blockers, propranolol use was found to be associated with higher rates of depression (Steiner, Friedhoff, Wilson, Wecker, & Santo, 1990). However, many studies have not been able to control for other confounding variables, such as use of benzodiazepines, which have been correlated with depression symptomatology (Bright & Everitt, 1992).

In a meta-analysis regarding the correlation of beta-blockers with depressive symptoms, research demonstrated that most patients do not experience depressive symptoms while taking beta-blockers and that possible depressive symptoms mainly arise after long-term use (Stoudemire et al., 1984). Therefore, future research may be directed toward monitoring the correlation of long-term use of beta-blockers with depressive symptoms, in addition to controlling for the use of other concurrent medications. Specifically, past research regarding quality of life and psychosocial adjustment of children and adolescents diagnosed with congenital heart disease has demonstrated a potential overall lower quality of life and is associated with a risk of developing behavioral problems (Mussatto et al., 2014).

Anxiety and Quality of Life of Children Diagnosed with LQTS

Children born with LQTS face physical challenges and restrictions, coupled with psychosocial obstacles and adjustments beginning early in their lives. Quality of life is a broad term used to define multidimensional aspects of individuals' lives that contribute to their overall enjoyment and happiness (Wallander, Schmitt, & Koot, 2001). These dimensions are composed of social, emotional, cognitive, physical, and spiritual aspects. Uzark et al. (2008) found that children diagnosed with congestive heart disease have a significantly lower quality of life as compared to same aged, healthy peers.

Caretakers and family members may struggle with the volume of financial responsibility and emotionally draining daily obligations associated with caring for a child diagnosed with a congenital heart defect (Bellinger & Newburger, 2010). Depending on age at diagnosis and level of cognition, children diagnosed with congenital heart disease may notice increased stress and worry at home. Specifically, children may not fully understand their condition and, as a result, feel restricted from activities and events that their same-aged peers partake in. Research has found that despite the successful use of beta-blocker medication, a small number of cardiac arrests and sudden deaths occur each year in individuals diagnosed with LQTS (Moss et al., 2000). The greatest risk factors for experiencing sudden cardiac death include recent syncope, individual corrected QT interval (QTc) measurements, and gender (Hobbs et al., 2006). These statistics may weigh heavily on parents and caretakers, as the stress of their children experiencing a sudden cardiac arrest or death is a constant concern.

The American College of Cardiology recommends that parents should decide whether or not they will allow their children diagnosed with LQTS to participate in recreational sports (Aziz et al., 2015). Participation in recreational sports and exercise has been regarded as the most significant trigger for cardiac-related episodes in many LQTS subtypes (Schwartz et al., 2009). However, research regarding the lower quality of life in children diagnosed with LQTS has led to medical professionals allowing parents and children to make an informed decision regarding participation in sports. Expert health professionals have warned against participation in physically demanding sports and recreational activities for individuals with certain variants of LQTS and instead recommend low-intensity sports and activities. In order to safely participate in these activities, research has suggested that patients with LQTS be supplied with plenty of water and electrolytes, follow perfect compliance with prescribed medication, and have access to an automated external defibrillator at all times. Therefore, caretakers and family members must be cognizant of not only the physical effects on their children living with LQTS, but also the mental health implications that their children must face daily in participating in activities that are beneficial to their quality of life, but also are life threatening.

Impact of living with a chronic illness. In the Ontario Child Health Study, 3,294 children aged 4 to 16 years who had been diagnosed with chronic illnesses were surveyed to find the likelihood that they would later develop psychiatric disorders and adjustment problems (Cadman et al., 1986). The study found that children and adolescents diagnosed with a chronic illness or various life-threatening medical conditions were at a higher risk than healthy, same-aged peers for developing psychiatric disorders and/or social-adjustment problems. The study was categorized into age- and sex-adjusted risks for mental health conditions and found that children with chronic illnesses that caused a disability were 3 times as likely as children with chronic illnesses without a disability to develop social-adjustment problems and/or mental health conditions. Taken together, children diagnosed with a chronic medical condition that causes a disability seem to experience a decline in their quality of life, possibly having further implications on their overall mental health and well-being.

Quality of life and psychological adjustment. The majority of research involving the quality of life and psychological adjustment in children diagnosed with congenital heart disease has utilized the Pediatric Quality of Life Inventory (PedsQl) in Children with Heart Disease (Latal, Helfricht, Fischer, Bauersfeld, & Landolt, 2009). Children with congenital heart disease are usually divided into two separate categories, those who have had open-heart surgery and those who are managed by medication. A meta-analysis conducted by Latal et al. (2009) found that children who underwent open-heart surgery because of a congenital heart disease diagnosis are at risk for negative effects to their quality of life and for psychological maladjustment. Additionally, parents of children diagnosed with congenital heart disease reported psychological maladjustment. Research has demonstrated the trend of an impaired quality of life and greater psychological maladjustment rising in correlation with a congenital heart disease diagnosis (Uzark et al., 2008). Thus, differentiating the side-effects of beta-blockers from the sole impact that a diagnosis of congenital heart disease has on a patient has proved to be difficult. At this time, research regarding the influence of cognitive side-effects of beta-blockers on the quality of life of an individual is limited.

Chapter 3: Research Question and Hypotheses

Research Question

Do children diagnosed with LQTS demonstrate measurable psychosocial and neuropsychological side-effects associated with long-term beta-blocker use?

Hypotheses

LQTS is a chronic illness often diagnosed in children and adolescents that may affect executive functioning and psychosocial well-being. The present study sought to evaluate the possible evidence of executive functioning difficulties and psychosocial maladjustment in children and adolescents diagnosed with LQTS. This pilot study examined through tailored test batteries whether any measurable neuropsychological and psychosocial side-effects may be associated with long-term use of beta-blocker medication through tailored test batteries.

H1: The participants would demonstrate inefficiencies in various areas of executive functioning, such as working memory, visual-spatial skills, and academic achievement.

H2: The participants would demonstrate psychosocial adjustment differences as compared to same-aged, healthy peers.

Chapter 4: Method

Design

A nonexperimental, exploratory case study design was used to provide detailed case studies of pediatric patients diagnosed with LQTS and prescribed beta-blocker medication on a long-term basis, with specific inclusion criteria. The following chapter examines use of this research design, inclusion/exclusion criteria, and procedure.

Participants and Setting

The study was approved by the Institutional Review Board of Philadelphia College of Osteopathic Medicine (PCOM). Parents signed an informed consent form for themselves and their children, and the participants signed an assent form. The study was conducted on site in a private room at PCOM's Center for Brief Therapy.

Procedure

Parents who were interested in their children's participation in the study were contacted by the investigator via e-mail and phone. Families were given time to ask any questions regarding the evaluation, compensation, and optional feedback session. At this time, the participant engaged in a brief, structured interview to determine the child's eligibility for study participation, as well as to build a case profile for the child. The questions were tailored by the investigator with advisement from the supervising psychologist and were directly related to the inclusion and exclusion criteria of the current study. The structured interview with the participant's parents lasted between 15 to 20 minutes. Families who qualified for the evaluation were informed after the conclusion of the structured interview and were scheduled for a mutually convenient evaluation time for the participant and the investigator. Parents of the participants were contacted prior to their day of examination by e-mail to remind them of the date, time, and location of the evaluation, as well as to answer any further questions. The investigator gave a $100.00 Visa gift card to each participant at the end of each examination day as an incentive for him or her to participate and stay through the entirety of the testing. Informed consent and assent were obtained for each participant at the beginning of the evaluation day. The entirety of each evaluation was video recorded using SIMULATIONiQ at the Center for Brief Therapy at PCOM. The investigator maintained close contact with supervising psychologist Dr. George McCloskey, Ph.D., who is a school psychologist and national expert in psychological testing. Table 1 provides information about the participants.

Table 1

Summary of Demographic and LQTS Information

Participant	Age in yrs	Grade in school	LQTS type	Age at diagnosis	Years prescribed beta-blockers	Compliance with medication	Family history	Significant educational history (e.g., past or current IEP; 504 plan)	Previous psychological testing
M31F	11	6	I	6	5.5	100%	Yes	Yes	Yes
M03M	16	12	II	12	6.5	100%	Yes	Yes	Yes
J06F	9	4	II	Birth	9	100%	Yes	Yes	Yes

Evaluation Day

All participants selected a morning evaluation session, with start times ranging from 8:00 to 10:00 a.m. Upon arrival, the participant and his or her parent were met in the lobby of PCOM and were escorted to a private room in the Center for Brief Therapy. The investigator explained the informed consent and assent to both the participant and his or her parent and obtained signatures. At this time, the investigator filed the informed consent and assent documents and distributed the Pediatric Cardiac Quality of Life Inventory (PCQLI) form for the parent to fill out in the waiting room of the Center for Brief Therapy. The parent remained in the waiting room until the conclusion of the evaluation session to ensure proper test administration for the participant.

All assessments on the evaluation day were administered by the investigator, who is a fifth-year clinical psychology doctoral candidate at PCOM, under the supervision of a clinical psychologist who is an expert in the test measures used. Throughout the evaluation day, the participants were administered several measures that addressed various domains of their overall mental health and cognitive functioning. The following measures were administered: the Wechsler Intelligence Scale for Children: Fifth Edition (WISC-V), the Wechsler Individual Achievement Test: Third Edition (WIAT-III), the Wide Range Assessment of Memory and Learning: Second Edition (WRAML2), the Delis-Kaplan Executive Function System (D-KEFS), the Grooved Pegboard Test (GPT), the Children’s Depression Inventory: Second Edition, Self-Report (CDI-2), the Screen for Child Anxiety Related Disorders CHILD Version (SCARED), the Pediatric Cardiac Quality of Life Inventory (PCQLI) Child/Adolescent Form and Parent of Child/Adolescent Form, with several subtests administered from each measure. In the morning session, the WISC-V, WIAT-III, and WRAML2 were administered in consecutive order. The individuals underwent testing until approximately noon and were then offered a lunch/snack break. In addition to the lunch/snack break, the individuals were allowed to take short stretch breaks, with individuals using age-appropriate behavioral reinforcements, such as stickers, iPad time, and pie charts showing tests completed/tests remaining. Built-in breaks and behavioral reinforcements were used to address various levels of test fatigue and potential attention issues, as inadequate effort is a major factor in determining the validity of neuropsychological test results (Vickery et al., 2001). The assessments were administered in a private room at PCOM's Center for Brief Therapy. Each of the three participants was exposed to the same conditions and had equal treatment and instruction pre and post completion of tests. To protect the integrity of the assessments, individuals were not briefed beyond any discourse that the assessment administration manuals instruct.

After the 30-minute lunch break, the afternoon testing session began. After lunch, the D-KEFS, GPT, CDI-2, SCARED, and PCQLI Child Form were administered in consecutive order. Upon completion of the afternoon tests, the participants were dismissed and informed again of the optional feedback session. All parents of participants expressed interest in the feedback session and thus were informed that they would be contacted by the investigator in the following days to schedule a mutually convenient date to meet for a 1-hour optional feedback session to discuss results of the evaluation with the investigator and supervising assessment psychologist, Dr. George McCloskey. The investigator then gave the $100.00 Visa gift card, as well as a $5.00 parking voucher, to the participant. The investigator then placed all assessment data in a locked box to preserve confidentiality and downloaded the videotaped evaluation session, which was kept on an encrypted flash drive. No identifying information was used on any of the test protocols, as all participants were administered a unique identification code and pseudonym.

Data Collection

The initial recruitment/screening process took place during the summer months of 2018 (i.e., May-July). The data collection portion of the study (i.e., when the assessments were administered to participants) took place over several weeks, with one patient scheduled each week for testing. In the days following the evaluation session, parents were contacted regarding scheduling their optional feedback session. Two parents selected a feedback session via conference call, while one parent selected an in-person feedback session. All three of the participants' parents were scheduled for their feedback session within 1 or 2 weeks of their child's evaluation session. Prior to meeting with participants' parents for the feedback session, the investigator and Dr. McCloskey met in person to discuss the results from each participant's evaluation session and to develop a format for the presentation of results. Each feedback session lasted approximately 60 minutes and was presented to the parents in a similar format, with a portion at the end dedicated for a question-and-answer period. The investigator distributed copies of the test appendix to each parent at the feedback session in case of further need of the data and left contact information in order to answer any questions and comments the parents/guardians may have in the future.

Chapter 5: Results

All children were given unique codes and pseudonyms to protect their identities and to maintain confidentiality. Participant M31F was known as “Sam,” Participant M03M was known as “Tim,” and Participant J03F was known as “Jade.”

Background: Participant M31F/ “Sam”

Sam was an 11-year-old girl entering the sixth grade at the time of the evaluation. Sam was formally diagnosed with Type I LQTS at age 6 years, with physical symptoms, such as heart palpitations, observed as young as 5 years of age. At the time of the evaluation, Sam had been taking nadolol, with a reported 100% compliance rate for 5.5 years. Familial history was significant for LQTS, as the biological father was reported to be a gene carrier for LQTS. No other immediate or extended family members had been formally diagnosed with LQTS, and the participant reportedly did not take any other prescription or over-the-counter medications. No other medical/mental health diagnoses were reported. Sam was reported to be asymptomatic since being prescribed nadolol. Educationally, Sam had an active individualized educational program (IEP) for English and language arts studies that had been implemented in the first grade. At the time of the evaluation, the IEP was reportedly being tailored to meet the participant’s educational needs in written expression. Sam underwent a psychoeducational evaluation in the fall of the first grade but had not participated in any other testing. Relevant results from the psychoeducational evaluation described difficulty with pronouncing nonsense words. Sam’s parent revealed a family history significant for dyslexia (i.e., biological father). No behavioral issues or complaints were reported by the participant’s parent, though Sam’s parent provided that the participant “does not like feeling different” and going to see the electrocardiologist is not an enjoyable experience for the participant. Sam reportedly enjoyed playing basketball and the violin and was reportedly beginning color guard in the fall of 2018.

Evaluation Results: Participant M31F/ "Sam"

Sam arrived early on the evaluation day and took her prescribed nadolol at 8:30 a.m. Sam's intellectual abilities were found to be intact overall and within the Average range (55^{th} percentile), demonstrating a significant strength within the Processing Speed Index (PSI). Specifically, Sam's overall processing speed was found to be within the Extremely High range (98^{th} percentile), indicating her above-average ability to quickly and correctly scan, sequence, and discriminate visual information. Further, Sam demonstrated some variability at the subtest level among separate skill sets. Specifically, though she demonstrated above average in expressive word knowledge skills in the Vocabulary subtest (75^{th} percentile), Sam demonstrated difficulty with her untimed visual-pattern analysis skills in the Matrix Reasoning subtest, scoring within the Very Low range (5^{th} percentile) when compared to same-aged peers. The Matrix Reasoning subtest involves identifying a missing portion of an incomplete visual matrix from one of five response options. This particular subtest assesses one's abstract and inductive reasoning to perceive logical sequences and patterns to complete an incomplete matrix. However, performance on this subtest is sensitive to effort and sustained attention at the particular time of evaluation.

Sam's performance on both immediate recall for contextualized (i.e., meaningful, organized) verbal information as well as delayed recall for the previously presented information in story format was found to be within the overall Average range for her age (50^{th} to 75^{th} percentile). Additionally, Sam was adequately able to encode, store, and later recognize contextual verbal information presented in a forced-choice format at an age-appropriate level

(84th percentile). Similarly, Sam was able to efficiently encode, store, and immediately retrieve visual information presented in a picture format at an age-appropriate level (25th percentile). She was able to later recognize this previously presented visual information in a forced-choice, cued format efficiently (37th percentile). Further, scores gathered from Sam's brief academic screening, which included her ability to sound out words increasing in complexity, to sound out nonwords/ word decoding skills, to write mathematical calculations under untimed problems, and to spell dictated letters, blends, and words, were of no concern. Sam demonstrated no difficulties with her fine-motor and eye-coordination skills, as evidenced by her above-average ability to manipulate and rotate small pegs to fit into the next appropriate slot as quickly as possible with both her right (87th percentile) and left hand (87th percentile). Sam demonstrated no concerns regarding her executive functioning skills in several key areas, including her visual scanning, number and letter sequencing, inhibition of automatic responses, and visual-motor speed (75th to 91st percentile). Additionally, Sam was able to verbally generate words from phonemic and semantic categories, as well as to demonstrate flexibility in approach during these tasks sensitive to executive functioning (37th to 95th percentile).

Behaviorally, Sam reported no clinically significant depressive thoughts or symptoms typically associated with depression and anxiety on either the CDI-2 or SCARED inventories. Further, Sam rated herself within the average limits regarding perception of her personal quality-of-life outlook, which was congruent with her mother's responses. Behavioral observations were significant for the participant being outgoing, talkative, and engaging with the investigator. Specifically, Sam asked the investigator questions about her life, as well as expressed distaste in a particular task she found challenging. Overall, the participant was a very hard working and friendly young girl.

Background: Participant M03M/ "Tim"

Tim was a 16-year-old boy entering the 12th grade at time of evaluation. Tim was reportedly diagnosed with LQTS Type II and began taking nadolol at age 12 years. He was reported to be 100% compliant with medication and was asymptomatic at time of participation. Tim's father reportedly was a carrier for the gene mutation associated with LQTS. Educationally, Tim was diagnosed with a learning disability in kindergarten and was eligible for an IEP, though no specific information regarding the services was provided nor was it currently active at the time of the current evaluation. Tim's mother reported no behavioral issues or concerns for the participant.

Evaluation Results: Participant M03M/ "Tim"

Tim arrived early on the evaluation day, which was scheduled for a Saturday morning. Upon arrival, Tim's mother believed her son to be quite fatigued, as he had been working a summer job throughout the week. Tim's overall intellectual abilities were found to be within the High Average range (75th percentile), with many demonstrated strengths at a subtest level within his expressive word knowledge (84th percentile), ability to analyze and synthesize abstract information (95th percentile), quantitative and logical visual reasoning (75th percentile), short-term auditory memory for number sequences (75th percentile), and processing-speed skills (91st percentile). Behavioral observations were noteworthy, as Tim needed much prompting and querying during the administration of the WISC-V. Specifically, administration of the WISC-V should take approximately 45 to 65 minutes in typical circumstances (Kaufman, Raiford, & Coalson, 2015). However, the duration of the WISC-V was approximately 90 minutes with Tim.

Tim's performance on both immediate recall for contextualized (i.e., meaningful, organized) verbal information as well as delayed recall for the previously presented information in story format was found to be within the overall Average range for his age (75th percentile overall). Additionally, Tim was adequately able to encode, store, and later recognize contextual verbal information presented in a forced-choice format at an age-appropriate level (50th percentile). Tim was able to efficiently encode, store, and immediately retrieve visual information presented in a picture format at an age-appropriate level as well (37th percentile). He was able to later recognize this previously presented visual information in a forced-choice, cued format efficiently (37th percentile). Further, Tim scored higher than expected for his age on a brief, academic screening, which included his ability to sound out words increasing in complexity, sound out nonwords/ word decoding skills, write mathematical calculations under untimed problems, and spell dictated letters, blends, and words. Specifically, Tim was within the Superior range (98th percentile) for his age group in his spelling skills, and within the Above Average range in basic word reading, word decoding, and written mathematical calculation skills. Tim demonstrated no difficulties with his fine-motor and eye-coordination skills during the GPT, scoring within the Average range for both hands (55th - 73rd percentile). Tim also did not display any concerns regarding his executive functioning skills in the aforementioned several key areas, including visual scanning, number and letter sequencing, inhibition of automatic responses, and visual-motor speed (37th - 75th percentile). Additionally, Tim was able to verbally generate words from phonemic and semantic categories, as well as demonstrate flexibility in approach during these tasks sensitive to executive functioning (50th - 63rd percentile).

Behaviorally, Tim reported no clinically significant thoughts or symptoms typically associated with depression on the CDI-2. However, Tim did endorse various symptoms typically associated with Generalized Anxiety Disorder, as captured by the SCARED. Specifically, Tim endorsed “Very True or Often True” for one prompt, “Somewhat True or Sometimes True” for

22 prompts, and "Not True or Hardly Ever True" for 18 prompts. Overall, most of Tim's endorsements were most closely related to Generalized Anxiety Disorder (cutoff score of 9 needed, actual score of 9 reported) and Social Anxiety Disorder (cutoff score of 8 needed, actual score of 7 reported). Next, Tim and his mother both rated Tim within the average limits regarding his quality of life, with no heightened concerns. Behavioral observations were significant for the participant being quite shy and reserved at the beginning of the evaluation morning and demonstrating a higher level of comfort talking with the investigator toward the end of the day. Overall, though, the participant needed much prompting at the beginning of the evaluation session but seemed to relax into the evaluation as the day continued.

Background: Participant J03F/ "Jade"

Jade was a 9-year-old girl entering the fourth grade at the time of the evaluation. Jade was formally diagnosed with Type-II LQTS in utero (approximately 6 months into duration of pregnancy). Thus, Jade reportedly was immediately prescribed propranolol at birth, which she continued taking until she was 3 years old. Jade's specific beta-blocker was then switched to nadolol, which she reportedly takes with 100% compliance at present. Regarding familial history, Jade's mother is also diagnosed with Type-II LQTS. Further, Jade's maternal aunt passed away from complications related to LQTS, which was diagnosed posthumously. Jade's mother reported that all medical symptoms associated with LQTS were well managed for the participant at time of evaluation. Educationally, Jade was reported to have an active IEP for difficulties in reading and math. Jade personally reported that her favorite subject was art. No behavioral issues were reported at the time of evaluation.

Evaluation Results: Participant J03F/ "Jade"

Jade was evaluated over the course of a morning and extending into the early afternoon. Her overall intellectual abilities were found to be within the Average range (47th percentile), with above-average strengths in her untimed visual pattern analysis skills (75th percentile) and visual perceptual motor speed (75th percentile) domains. Her lowest subtest score, Visual Puzzles, was within the Low Average range (16th percentile), indicating some inefficiency within her visual-reasoning and problem-solving abilities.

Though Jade's immediate recall for contextualized (i.e., meaningful, organized) verbal information was within the Borderline to Low Average range (9th percentile), she was able to increase her score and remember more details about a story after a delay (25th percentile) and to recognize the previously presented information in a forced-choice, cued format (25th percentile). This response pattern indicates an inefficiency within her initial storage of verbal information presented in a story format. However, Jade was able to encode, store, immediately retrieve, and recognize visual information presented in a picture format at an age-appropriate level (50th - 91st percentile). Scores gathered from Jade's brief academic achievement screener were significant for a lower-than-expected score as compared to same-aged peers within her phonemic word decoding of nonword abilities (16th percentile), which was expected per her mother's report. All other academic areas assessed were found to be average (e.g., sounding out words increasing in complexity, writing mathematical calculations, and spelling dictated letters, blends, and words; 25th - 50th percentile). Jade demonstrated no difficulties with her fine-motor and eye-coordination skills, scoring within the Average range (39th - 50th percentile) for both hands. Additionally, Jade displayed some areas of inefficiency within her executive functioning skills (e.g., basic visual scanning, cognitive flexibility, inhibition of automatic responses, and maintaining a cognitive set). Specifically, Jade completed number- and letter-sequencing tasks at a much slower speed than expected for her age group (overall <1st percentile), while demonstrating errors in connecting the letters of the alphabet in correct order. Furthermore, Jade's performance on a verbal-fluency task that required her to generate words beginning with a specific letter of the alphabet and then by specific categories fell within the Low Average to Average range (16th - 63rd percentile). Jade's performance on an additional administered task reliant upon systematic retrieval of lexical items, monitoring, cognitive switching (flexibility), as well as establishing and maintaining the cognitive set was within the Low Average range (16th percentile). Overall, Jade's response profile indicated difficulties with phonemic fluency, which, as aforementioned, was consistent with parent and educational reports.

Behaviorally, Jade endorsed no clinically significant depressive thoughts or symptoms on the CDI-2 but did endorse many symptoms associated with an Anxiety Disorder on the SCARED. Specifically, Jade endorsed "Very True or Often True" for 18 prompts, "Somewhat True or Sometimes True" for 15 prompts, and "Not True or Hardly Ever True" for 8 prompts. Specifically, a total score of25 or greater may indicate the presence of an Anxiety Disorder on the SCARED; Jade scored a 51. Further, Jade's scores were also indicative of Generalized Anxiety Disorder, Panic Disorder or Significant Somatic Symptoms, Separation Anxiety Disorder, Social Anxiety Disorder, and Significant School Avoidance. However, one should note that the investigator had to modify the administration of the SCARED because of the participant's reading-ability level. The investigator read each question aloud to the participant and also placed a physical Likert scale in front of the participant for selection clarification. Overall, the results illustrate that the participant experienced significant anxiety in several areas.

However, Jade and her mother did not report any clinically significant findings related to their perception of the participant's quality of life.

Chapter 6: Discussion

This study presents the findings from an exploratory case study aimed at assessing neuropsychological, mental health, and quality-of-life domains in children and adolescents diagnosed with LQTS and taking beta-blocker medication on a long-term basis. The primary purpose of the study was to assess, detail, and conceptualize any neuropsychological, mental health, and quality-of-life differences in this group of children and adolescents, as compared to the statistical normative data of same-aged, healthy peers. Previous research has indicated that long-term use of beta-blocker medications may affect users in their executive functioning skills, mental health, and behavior at home (Lawley et al., 2009). Though the current study is unable to conclude that results of the current study support the hypotheses and directly link long-term beta-blocker use with score differences, the findings demonstrated overall neuropsychological, mental health, and quality-of-life differences in the children and adolescents who participated in the examination. Therefore, the results that follow discuss demonstrated differences within each assessed domain (i.e.., neuropsychological, mental health, quality of life) when compared to the normative data of same-aged peers.

Intellectual Functioning Differences

Two of the three participants demonstrated some inefficiencies within specific subtests on the WISC-V, specifically on the Block Design, Visual Puzzles, and Matrix Reasoning subtests. These lower-than-expected scores are described as inefficiencies rather than as weaknesses, as both participants scored within the Average range on other subtests included within the same measured domain. Specifically, Sam scored within the Low Average range (16^{th} percentile) on the Block Design subtest, while scoring within the Average range (63^{rd} percentile) on Visual Puzzles. Similarly, while Jade scored within the Average range on Block Design (37^{th}

percentile), she scored within the Low Average range (16th percentile) on Visual Puzzles. This pattern of variability within indices is consistent with typical profiles of children with executive dysfunction, specifically automaticity for tasks reliant upon problem-solving reasoning skills (McCutchen, 1988). Automaticity is defined as an innate, rote cognitive process that enables one to automatically attend to and successfully sustain completion of a task to the best of one's ability (Gray, 2004). Additionally, the cognitive process of automaticity is inextricably linked with self-regulation and self-management (Gawrilow & Gollwitzer, 2008), areas in which the investigators hypothesize to be areas of weakness for both Sam and Jade. Sustained automaticity throughout the completion of novel, increasingly complex tasks often presents as a challenge for children previously diagnosed with learning disabilities and attention-deficit hyperactivity disorder (ADHD; Potter, 2017). Both Sam and Jade were previously diagnosed with specific disabilities in similar areas (e.g., Sam for written expression, basic reading skills, reading fluency, and reading comprehension, and Jade reportedly for reading and mathematics). Thus, inefficiencies within the cognitive processes of automaticity, self-regulation, and self-management are presumed to influence scholastic performance of both participants, further discussed later in a relevant paragraph. Table 2 provides participants' scores on the WISC-V.

Table 2

Intellectual Functioning: Wechsler Intelligence Scale for Children – Fifth Edition (WISC-V)

Subtest	M31F	M03M	J03F
Vocabulary	12	13	10
Similarities	9	11	10
Block Design	7	10	9
Visual Puzzles	11	15	7
Matrix Reasoning	5	11	12
Figure Weights	10	12	8
Digit Span	11	12	8
Picture Span	10	10	8
Symbol Search	13	14	9
Coding	18	11	12

Note. Values shown are scaled scores.

Academic Achievement Differences

All three participants generally scored at or above the expected range on brief measures assessing general academic achievement. However, Jade demonstrated scores within the Low Average range (16th percentile) on the Pseudoword Decoding subtest of the WIAT-III, consistent with parent report of a history of phonological awareness difficulties. One should note that automaticity is integral in speech development, specifically in the language processes necessary in reading and writing (Potter, 2017). Though Jade scored within the lower end of the average range in her ability to orally decode increasingly difficult nonsense words, the influence that even minor inefficiencies may have on foundational skills, such as reading and writing, cannot be discounted. Table 3 provides participants' scores on the WIAT-III.

Table 3

Academic Achievement Screener. Wechsler Individual Achievement Test-Third Edition (WIAT-III)

Subtest	M31F	M03M	J06F
Word Reading	105	121	90
Pseudoword Decoding	100	125	85
Spelling	106	131	96
Numerical Operations	124	126	100

Note. Values shown are standard scores.

Memory Differences

Similar to results derived from the measures on the academic achievement test, Jade also displayed Borderline to Low Average range (9th percentile) abilities in immediate recall for verbal information (i.e., short-term/working memory). These results are hypothesized to be related to inefficiency within Jade's central executive, namely efficient storage of information (Engle & Kane, 2004). Efficient storage of information relies on inhibiting irrelevant, interfering information, as well as on maintaining the cognitive set (e.g., focusing on the current task) and sustaining attention. Overall, Jade demonstrated the most inefficiencies on measures dependent upon the central executive, as compared to both Sam and Tim, who demonstrated no clinically significant findings in both their short-term and long-term memory for both visual and verbal information. Table 4 provides participants' scores on the WRAML2.

Table 4

Memory Tasks: Wide Range Assessment of Memory and Learning-Second Edition (WRAML2)

Subtest	M31F	M03M	J06F
Story Memory	10	12	6
Story Memory Recall	12	12	8
Story Recognition	13	10	8
Picture Memory	8	9	10
Picture Memory Recognition	9	9	14

Note. Values shown are scaled scores.

Executive Functioning Differences

Consistent with prior domains, neither Sam nor Tim demonstrated any clinically significant findings within their executive functioning abilities. However, Jade demonstrated several inefficiencies within her ability to rapidly generate words by letter following specific rules, in addition to her cognitive flexibility accuracy and speed during a verbal switching task. Additionally, Jade demonstrated difficulties in her basic visual scanning, cognitive flexibility, and inhibition, as well as in establishing and maintaining cognitive set and working memory (i.e., recalling the sequence of the alphabet in proper order during a timed visual-motor task). Specifically, Jade's performance on the number-sequencing task was accurate but slower than expected (<1st percentile), indicating a less efficient processing speed than that of same-aged peers. Jade also demonstrated a much slower than expected response style while committing two sequencing errors on a letter-sequencing task reliant on her ability to accurately recall the sequence of the alphabet (<1st percentile). This response pattern is consistent in children with specific language-processing deficits who do not yet have the alphabetic sequence committed to rote memory, formally known as verbal automaticity (Stern & Morris, 2012). Jade's performance on the WIAT-III subtest, Pseudoword Decoding, is consistent with her performance on executive functioning tasks dependent on verbal abilities. Thus, Jade's performance supports literature associating deficits in reading and language abilities with inefficiencies within tasks dependent upon executive functioning (e.g., verbal working memory, processing speed, and response inhibition; Willcutt, Pennington, Olson, Chhabildas, & Hulslander., 2005). Table 5 provides participants' scores on the D-KEFS.

Table 5

Executive functioning Tasks: Delis-Kaplan Executive Function System (D-KEFS)

Subtest	M31F	M03M	J06F
Verbal Fluency Test			
Letter Fluency	11	11	7
Category Fluency	15	10	11
Category Switching Total Correct	9	10	7
Category Switching Total Switches	14	11	5
Trail Making Test			
Visual Scanning	13	10	4
Motor Speed	12	9	10
Number Sequencing	13	11	1
Letter Sequencing	14	12	2
Number-Letter Sequencing	12	11	11

Note. Values shown are scaled scores.

Fine-Motor-Skills Differences

Every participant demonstrated solidly intact and age-appropriate fine-motor and dexterity skills on a grooved pegboard task reliant on visual-motor and fine-motor coordination for both dominant and nondominant hands. Table 6 provides participants' scores on the GPT.

Table 6

Fine-Motor Tasks: Grooved Pegboard Test (GPT)

Subtest	M31F	M03M	J06F
Right Hand	117	102	100
Left Hand	118	109	96

Note. All participants were right-hand dominant. Values shown are standard scores.

Mental Health Differences

All participants endorsed average or lower symptoms associated with depression as compared to same-aged peers on the CDI-2, Self-Report. However, some participants indicated some clinically significant levels of anxiety on the SCARED CHILD Version. Though Sam did not endorse any clinically significant symptoms associated with anxiety, Tim and Jade did endorse several borderline clinically significant and clinically significant anxiety symptoms. Specifically, Tim was found to endorse clinically significant symptoms associated with generalized anxiety disorder, and Jade was found to endorse clinically significant symptoms associated with panic disorder/somatic symptoms, generalized anxiety disorder, separation anxiety disorder, social anxiety disorder, significant school avoidance, and total anxiety score. These scores are consistent with prior research demonstrating that children diagnosed with heart rhythm disorders, as well as congenital heart disease, experience significantly higher levels of anxiety than same-aged, healthy peers (Oliver et al., 2018). Tables 7 and 8 provide participants' scores on the CDI-2, Self-Report and SCARED.

Table 7

Behavioral Questionnaires:
Children's Depression Inventory-Second Edition, Self-Report (CDI-2)

Indices	M31F	M03M	J06F
Emotional Problems	48	50	51
Negative Mood/Physical Symptoms	46	55	55
Negative Self-Esteem	51	44	44
Functional Problems	≤40	44	54
Ineffectiveness	≤40	44	53
Interpersonal Problems	42	42	52
Total Score	44	47	53

Note. Values shown are *t* scores.

Table 8

Behavioral Questionnaires:
Screen for Child Anxiety Related Disorders (SCARED) CHILD Version

Indices	M31F	M03M	J06F
Panic Disorder/Somatic Symptoms	1	5	12
Generalized Anxiety Disorder	0	9	9
Separation Anxiety Disorder	1	3	15
Social Anxiety Disorder	4	7	12
Significant School Avoidance	0	0	3
Total Score	6	24	51

Note. Values shown are total raw scores. A total score of ≥ 25 may indicate the presence of an anxiety disorder. Scores higher than 30 are more specific (see text).

Quality-of-Life Differences

Two of the three participants and their parents consistently endorsed unremarkable scores on the PCQL, indicating an overall high, self-perceived quality of life. These findings indicate that children and adolescents within the current study have experienced an overall comparable quality of life as compared to that of their same-aged, healthy peers. Psychometrically, the PCQLI generates three separate scores (i.e., total score, disease impact subscale, and psychosocial impact subscale), with the total score being out of a possible 100 points and the subscales totaling a possible 50 points each. Each participant's total score and subscale scores were consistent with their endorsements on the two-prior mental health questionnaires (i.e., CDI-2 and SCARED). Sam, Tim, and their parents endorsed scores consistent with an overall high self-perceived quality of life. Jade's scores were the most notable, as both the participant and her parent endorsed scores indicating that a LQTS diagnosis had adversely affected their quality of life (disease impact). Jade's parent also endorsed scores indicating the participant's diagnosis was psychosocially impactful. These findings were corroborated by Jade's parent's anecdotal reports of personal impact disclosed during the study eligibility interview (e.g., recent deaths of immediate and extended family members). Therefore, findings of the current study do not fully support the investigator's hypothesis involving children diagnosed with LQTS and lower overall scores on the PCQLI subscales, as only one participant endorsed overall lower scores on the PCQLI subscales as a result of significant psychosocial stressors related to her familial history related to LQTS. Past research on the PCQLI used with children diagnosed with LQTS has demonstrated that children often experience difficulties with internalizing their feelings (Czosek et al., 2016). Additionally, the presence of a cardiac device and any adversely experienced medication side-effects are associated with lower scores on the PCQLI. Overall, patients with LQTS and their parents report lower quality of life than do normal children secondary to physical and psychosocial factors. An increasing focus on the psychological well-being of these patients is needed in an effort to improve their quality of life. Table 9 provides participants' scores on the PCQLI.

Table 9

Behavioral Questionnaires:
Pediatric Cardiac Quality of Life Inventory (PCQLI)

Indices	M31F		M03M		J06F	
	Parent	Child	Parent	Adolescent	Parent	Child
Disease Impact	+37/50	+44/50	+45/50	+47/50	+30/50	+34/50
Psychosocial Impact	+39/50	+46/50	+50/50	+49/50	+35/50	+50/50
Total	+76/100	+90/100	+95/100	+96/100	+65/100	+84/100

Note. *Age 8-12 Form* used for M31F and J06F. *Age 13-18 Form* used for M03M. Higher scores are associated with a higher quality of life.

Implications

This case study contributes to medical literature related to the potential side-effects of a necessary medication used to treat a congenital heart disease through detailed neuropsychological profiles of children and adolescents aged 8 to 16 years. The data gathered from this study assist in developing a more complete understanding for medical professionals of the side-effects associated with beta-blocker use. Health professionals will now have access to detailed literature related to the cognitive and mental health side-effects associated with beta-blocker use in the pediatric population. Finally, educational personnel who work with individuals taking beta-blocker medications may further understand the inextricable link between foundational executive functioning deficits and academic achievement and will be able to refer individuals to proper remediation programs and educational assistance.

Evidence-based remediation programs include the use of CogMed©, a computerized system that targets inefficiencies within an individual's foundational executive functioning skills (i.e., working memory and processing speed) through games (Diamond & Lee, 2011). Aerobic exercise is also recommended for children with executive functioning inefficiencies, as aerobic exercise has been found to improve prefrontal-cortex function (Hillman, Erickson, & Kramer, 2008). However, this intervention may not be feasible for all children diagnosed with LQTS or other related heart rhythm conditions because of potential exercise restrictions for patients who have them. Thus, mindfulness training and yoga are suggested to aid in improvement of executive functioning skills, specifically in shifting and self-monitoring skills for children who may have exercise restrictions (Flook et al., 2010). A more informal yet effective classroom-based intervention is the adoption of scaffolding-based visual reminders before, during, or at the completion of a task that discretely remind or reinforce expectations for the student (Diamond, Barnett, Thomas, & Munro, 2007). For children with anxiety symptoms, the first-choice intervention is cognitive-behavioral therapy (CBT; Pereira et al., 2018). CBT is an effective therapy for anxious children, as the therapeutic modality aids in the development and implementation of healthy coping skills paired with anxious, intrusive thoughts as a means to cognitively restructure any maladaptive beliefs or avoidance patterns. Consistent and proper implementation of CBT by a mental health professional may aid in the reduction of an individual's anxiety symptoms through the promotion of autonomy in coping and problem-solving skills.

Limitations

This case study was small, with three participants recruited from a large metropolitan area in the northeastern area of the United States. Therefore, scores gathered from another area of the United States may yield different results from a more diversified sample of participants because of demographics and educational-resource funding in school systems. In addition, age of participants was restricted (i.e., ages 8-16 years) to account for both long-term use of beta-blocker medication, while still being considered a child or adolescent. The inclusion of a broader age range may have demonstrated additional differences in the aforementioned domains resulting from developmental, social, and emotional changes that are seen in children and adolescents throughout the lifespan. More specifically, the study inclusion criteria may have limited the generalizability of results, as is typically seen with case study research. Various factors, such as diversified ages, socioeconomic statuses, races, and genders, also may have rendered different results. Additionally, targeting and attributing any cognitive differences from same-aged peers to beta-blocker use alone is difficult. Countless factors may affect a child's or adolescent's test performance on neuropsychological measures that may be unrelated to the cognitive side-effects of long-term use of beta-blocker medication. Some of these factors include genetics, environment, and comorbid diagnoses, such as specific learning disabilities, ADHD, and autism spectrum disorder, as the symptomatology of many of these presentations overlap (Duff & Sulla, 2015. Furthermore, neuropsychological, mental health, and quality-of-life assessments and questionnaires are extensive. The use of another measure may provide different results in the future because of the wording of questions, the complexity of a subtest, and demonstrated attention span throughout the subtests. More specifically, the current study did not use a validity measure to account for possible inadequate effort by a participant. However, children and adolescents may demonstrate evidence of noncredible performance during neuropsychological assessment, thereby confounding and invalidating any estimate or representation of their true abilities (Kirkwood, Yeates, Randolph, & Kirk., 2012). To control for noncredible effort in future studies, investigators may consider using a performance validity measure, as well as carefully considering a participant's psychosocial history.

Differentiating side-effects associated with medication use versus a medical condition is an arduous task. Though adverse drug reactions reported by patients taking beta-blocker medication may be briefly inquired about and monitored at each appointment with their relevant healthcare providers, differentiating adverse drug reactions from a medical condition depends on fair and established assessment practices (Coleman, Ferner, & Evans, 2006; Marante, 2018). Currently, no guidelines have been established for the neuropsychological assessment of pediatric patients with LQTS taking beta-blocker medication. Typically, pediatric neuropsychologists reevaluate patients every 2 to 3 years, or when significant neuropsychological changes in an individual are suspected since the time of initial diagnosis (Annett, Patel, & Phipps, 2015). Thus, an established standard of care for the initial cognitive screening at the time of diagnosis and subsequent monitoring of potential neuropsychological changes by healthcare providers are suggested.

Future Directions

Case studies in clinical neuropsychology seek to further understand unique variables that may impact and alter an individual's neurodevelopmental trajectory (Baron, 2018). Thus, case studies may not only illustrate unique differences in individuals diagnosed with a variety of neurological conditions, complex medical diagnoses, and behavioral issues, but also dictate to the neuropsychology community the most appropriate measures in initial and follow-up evaluations. For example, unique medical conditions, including sickle cell disease, post-concussion syndrome, epilepsy, and mitochondrial dysfunction, have longstanding documented research regarding neuropsychological outcomes and guidance on appropriate test measures for neuropsychologists. At the time of the current study, pediatric neuropsychologists are increasingly involved in the initial evaluation and follow-up of individuals diagnosed with cardiac conditions (Cassidy et al., 2018. Thus, the body of research regarding congenital heart disease and cardiac conditions continues to grow rapidly through the understanding of brain development, neuropsychological outcomes, factors that may influence outcome variability, and implications for evaluation in these populations.

Future directions for study may include a more diversified sample (i.e., different races and ages) to more completely capture a broader range of individuals affected by cognitive side-effects of long-term beta-blocker use. In addition, a larger scale study including the collaboration of neuropsychologists in different metropolitan areas across the United States could collect and compare results using the same measures to gather further data on the cognitive side-effects of long-term beta-blocker use in order to contribute to aforementioned standardized guidelines for evaluation in these populations. Finally, a longitudinal study may trace neuropsychological, mental health, and quality-of-life changes over time with both large and small groups of individuals. The opportunity is significant for collaboration between neuropsychologists and cardiac health professionals to recruit individuals prescribed beta-blocker medication on a long-term basis and to study any self-reported and demonstrated cognitive side-effects in the rapidly growing integrated health domain.

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Appendix

Study Eligibility Questionnaire

1.) Participant's Relationship to Informant (e.g., biological parent, guardian, etc):____

2.) Type of LQTS:____

3.) Age Diagnosed: ____

4.) Amount of Time Taking Beta-Blockers: ____________________________________

5.) Type of Beta-Blocker Prescribed: ____

6.) Compliance Status with Medication: _______________________________________

7.) If Not Compliant with Medication, Explain: _________________________________

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____

8.) Familial Medical History Related to LQTS: _________________________________

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9.) Medical Symptoms Associated with LQTS: _________________________________

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10.) Educational History (e.g., 504 Plan, Individualized Educational Program (IEP), any difficulty with subjects, etc): ____

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11.) Neuropsychological or Psychoeducational Evaluation or Any Psychological Testing in the Past Year? ____

12.) If Yes, Please List Tests and Purpose of That Evaluation: ____________________

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13.) Behavioral History: ____

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14.) Miscellaneous Notes: ____

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