BIOPSYCHOSOCIAL COMPARISON OF ADHERENT VERSUS NONADHERENT MULTIPLE SCLEROSIS PATIENTS

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ABSTRACT

OBJECTIVE: Between 30-50% of patients with relapsing remitting multiple sclerosis (RRMS) prematurely discontinue disease modifying therapies (DMTs). Despite this, relatively little is known about clinical factors that may contribute to poor adherence in MS. This study sought to explore clinical characteristics associated with poor medication adherence among RRMS patients who have chosen to discontinue DMTs against medical advice. Specifically, we examined perceived social support, emotional functioning, and clinical disease-related characteristics in a group of nonadherent RRMS patients who discontinued DMTs against medical advice and a group of adherent RRMS who have taken at least 80% of prescribed DMT doses for two months preceding study enrollment.

METHODS: The current study recruited 50 adherent RRMS patients from an MS specialty clinic in the Midwest to demographically match an existing sample of nonadherent patients who participated in a recently completed clinical trial. Participants underwent a neurological exam and completed a battery of tests and questionnaires assessing social, emotional, and disease-related characteristics. The current study sought to achieve the following aims:

1. Examine differences in perceived social support between adherent and nonadherent RRMS patients. We hypothesized that nonadherent MS patients would report receiving less provider support and less social support than adherent MS patients.
2. Examine the role of depressive symptoms in patients deciding to discontinue DMTs against medical advice. We hypothesized that nonadherent patients would endorse more symptoms of depression and more frequently meet criteria for a major depressive episode than adherent patients.

3. Examine clinical disease-related characteristics between DMT adherent and nonadherent RRMS patients. We hypothesized that nonadherent MS patients would have greater disability than adherent patients.

RESULTS: The sample included 129 RRMS patients (50 adherent, 79 nonadherent). Adherent patients reported greater perceived autonomy support from their treatment providers than nonadherent participants, $F(1, 124) = 28.170$, $p < 0.001$, partial $\eta^2 = .185$ and exhibited less disability than nonadherent patients, $F(1, 124) = 4.251$, $p < 0.05$, partial $\eta^2 = 0.033$. No significant differences were identified in perceived social support, self-reported depressive symptoms, or clinical depression between adherent and nonadherent groups.

CONCLUSIONS: This was the first study to examine factors associated with nonadherence among RRMS patients who discontinued DMTs against medical advice. The results of this study suggest that greater perceived autonomy support from treatment providers may increase the likelihood of DMT adherence. These findings emphasize the important role of positive patient-provider relationships for improving medication adherence among RRMS patients who have prematurely discontinued treatment against medical advice. Results may inform future interventions aimed at improving treatment adherence among patients who demonstrate poor adherence, as well as those who prematurely discontinue DMTs against medical advice. Future research may want to elucidate the role of perceived provider autonomy support among nonadherent patients and explore interventions aimed at improving provider autonomy support.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the College of Arts and Sciences have examined a thesis titled "Biopsychosocial Comparison of Adherent and Nonadherent Multiple Sclerosis Patients," presented by Morgan B. Glusman, candidate for the Master of Arts degree, and certify that in their opinion it is worthy of acceptance.

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CONTENTS

TABLES

LIST OF ABBREVIATIONS

Multiple Sclerosis = MS

Central Nervous System = CNS

Major Histocompatibility Complex = MHC

Human Leukocyte Antigen = HLA

Epstein-Barr Virus = EPV

Relapsing Remitting Multiple Sclerosis = RRMS

Secondary Progressive Multiple Sclerosis = SPMS

Primary Progressive Multiple Sclerosis = PPMS

Progressive Relapsing Multiple Sclerosis = PRMS

Disease Modifying Therapies = DMTs

World Health Organization = WHO

CHAPTER 1

LITERATURE REVIEW

Multiple Sclerosis

Multiple Sclerosis (MS) is an autoimmune disease characterized by demyelination in the central nervous system (CNS). Lesions, or "scleroses," occur when the immune system erroneously attacks the myelin sheath surrounding axons in the CNS. Resulting symptoms commonly impact cognitive, emotional, and physical functioning and may include visual disturbance, numbness or tingling, weakness, fatigue, incontinence, sexual dysfunction, and depression (Crayton & Rossman, 2006; Poser, 1994). MS symptoms typically worsen with the progression of the disease and can interfere with aspects of daily living, often leading to reduced overall quality of life (Clavelou, Auclair, Taithe, & Gerbaud, 2009; Kobelt, Berg, Lindgren, Fredrikson, & Jonsson, 2006).

Affecting nearly 2.5 million people globally, MS is one of the most prevalent neurodegenerative diseases among young adults (Marrie et al., 2015). Disease onset generally occurs between the ages of 20 and 50 years-old (Sadovnick & Ebers, 1993), but has been reported in pediatric cases (Lulu, Julian, Shapiro, Hudson, & Waubant, 2014; Narula, Hopkins, & Banwell, 2015; Pena & Lotze, 2013; Turner, Sloan, Kivlahan, & Haselkorn, 2014) and older adults (Marrie et al., 2015). MS is most prevalent among Caucasian women of northern European ancestry.

Genetic and Environmental Influences. Although idiopathic in origin, studies suggest that MS may result from a complex interplay between genetic and environmental factors. The primary genetic factor associated with MS etiology is the major histocompatibility complex (MHC) (Chao et al., 2008). The MHC is a group of genes found in all vertebrates that code for cell surface proteins that support the immune system. In humans, these proteins are referred to as human leukocyte antigen (HLA). HLA enables the body to recognize and respond to the presence of antigens. This MHC-mediated communication appears to be disrupted in MS, as the body's immune system attacks its own tissue. Genome-wide association studies have also implicated non-MHC loci in MS (De Jager et al., 2009), but these genetic effects are thought to have minimal influence on disease susceptibility (Lincoln et al., 2009).

Predispositions to MS can be found in those with a family history of the disease. Research comparing heritable differences in MS showed increased susceptibility among individuals who have a first-degree relative with MS (2.5-5%), compared to those without relatives with MS (0.1%). For those with a family history of MS, vulnerability continues to increase with each additional first-degree relative with the disease. Twin studies also elucidate heritability in MS, as monozygotic and dizygotic twins vary in susceptibility to the disease (25.4% vs. 5.4 %, respectively) (Willer, Dyment, Risch, Sadovnick, & Ebers, 2003). This implicates other causal factors in MS because monozygotic twins share identical DNA yet lack equivalent rates of disease expression (Fagnani et al., 2015).

Environmental factors such as sun exposure, have been associated with disease development as well as prevalence of MS with respect to geography (Disanto et al., 2011; Ramagopalan et al., 2011; Simpson, Blizzard, Otahal, Van der Mei, & Taylor, 2011). Many studies suggest that rates of MS increase with greater distance from the equator (Koutsouraki, Costa, & Baloyannis, 2010; Pugliatti, Sotgiu, Solinas, Castiglia, & Rosati, 2001). Migration studies indicate that proximity to the equator matters most during the first fifteen years of life, as vulnerability to developing the disease appears unchanged in those who relocate after adolescence (Elian, Nightingale, & Dean, 1990; Hogancamp, Rodriguez, & Weinshenker, 1997). Another potential factor in the development of MS is the Epstein-Barr virus (EBV), which causes mononucleosis. Although EBV has been detected in approximately 90% of the general population, it is found in nearly 100% of the MS population (Ascherio & Munger, 2007; Haahr, Plesner, Vestergaard, & Hollsberg, 2004), suggesting associated increased risk with EBV-specific antibodies and the development of MS (Levin et al., 2005). Hygiene has been investigated as another possible factor influencing the development of MS. Decreased infection rates resulting from lack of exposure to pathogens correlate with increased incidence of autoimmune and allergic diseases (Fleming & Fabry, 2007).

Symptomology and Subtypes. MS is categorized into four subtypes indicating disease progression (F.D. Lublin & Reingold, 1996). Identifying a patient's subtype can help guide prognosis and treatment. MS is commonly diagnosed while patients are in the relapsing-remitting stage (RRMS, ~85%

of patients), which is characterized by intermittent episodes of disease activity, also referred to as "attacks," "exacerbations," or "flare-ups." These exacerbations are interspersed with periods of relative disease stability. Over time, the majority of RRMS patients develop a continuous worsening of disability that is the hallmark of secondary progressive disease (SPMS). Primary progressive MS (PPMS) occurs less often, affecting approximately 15% of patients. PPMS is marked by progressive decline from onset without periods of remission (Miller & Leary, 2007). A few patients experience progressive relapsing MS (PRMS) where frequent relapses are interspersed with gradually increasing disability from disease onset (Tullman, Oshinsky, Lublin, & Cutter, 2004).

Treatment. Without a cure for MS, early intervention is optimal for decreasing disease activity and reducing the probability of future decline (Freedman et al., 2013; Gold, Wolinsky, Amato, & Comi, 2010). Most disease modifying therapies (DMTs) are intended for RRMS patients. These medications have been shown to delay disease progression, reduce the development of new lesions up to 75%, and decrease clinical exacerbations by 50% (DiMatteo, 2004; Goodin, 2008; Sanchez-de la Rosa, Sabater, Casado, & Arroyo, 2012; Simon et al., 1998). Historically, DMTs were limited to intramuscular or subcutaneous injections, which commonly resulted in undesirable side effects, such as injection site reactions and flu-like symptoms. Now, thirteen DMTs have been approved by the U.S. Food and Drug Administration, offering new methods for administering medication, such as oral capsules and intravenous infusions. DMTs are preventive treatments that do not ameliorate current symptoms. This, along with possible adverse side effects (Minen & Karceski, 2011) and the uncertainty of future benefit, may cause patients to question the efficacy of their treatment (O'Rourke & Hutchinson, 2005; Rio et al., 2005).

Adherence

Adherence generally refers to one's capacity and willingness to follow healthcare providers' recommended treatments (Organization, 2003; Rand, 1993). Commonly preferred over 'compliance,' the term 'adherence' infers patient involvement in health care decision-making processes, which is thought to promote commitment to treatment (Berger, Liang, & Hudmon, 2005). Poor medication adherence is a

longstanding public health problem that limits the overall effectiveness of healthcare (Klauer & Zettl, 2008; Zullig et al., 2015). Negative implications of poor medication adherence include increased costs associated with medical complications, increased emergency room visits, increased hospitalizations, and poor health care outcomes (Seabury, Gupta, Philipson, & Henkhaus, 2014). Poor adherence is omnipresent among patients with chronic illnesses, which is likely a result of the unique demands of long-term care (L. Osterberg & T. Blaschke, 2005; Saini, Schoenfeld, Kaulback, & Dubinsky, 2009; Sokol, McGuigan, Verbrugge, & Epstein, 2005).

Chronic illness is identified by the World Health Organization (WHO) as permanent, disabling, irreversible, or requiring prolonged professional care (Organization, 2003). Some examples of chronic conditions include heart disease, diabetes, obesity, asthma, epilepsy, and MS. Chronic medical conditions are the leading cause of premature deaths worldwide (Organization, 2003) and account for nearly 2 million deaths in the United States annually (Milani & Lavie, 2015). Chronic illness is among the most prevalent and costly health-related issues, affecting nearly half of all adults in the US (approximately 120 million), including 30 million with comorbid chronic conditions (CDC, 2012). Up to half of all patients with chronic conditions prematurely discontinue prescribed medication regimens despite known benefits to treatment (Ferrari, de Sousa, & Castro, 2013; Harrison et al., 2013; Petri, Perez-Gutthann, Longenecker, & Hochberg, 1991; Sabate, 2003).

It is estimated that improved disease management and increased adherence to medication regimens would save roughly $290 billion annually (Lars Osterberg & Terrence Blaschke, 2005), subsequently reducing health care expenditures by approximately 13% (Cutler & Everett, 2010). Additionally, increasing the amount of prescriptions filled by 1% is projected to reduce Medicare expenses by an estimated 0.2% (Organization, 2003). However, previous attempts to increase accessibility to health care services appear ineffective, as challenges with adherence to appointments and treatments persist. The WHO has since suggested that interventions aimed at improving treatment adherence may prove more valuable than other major medical advances (Haynes, McDonald, & Garg, 2002). Despite the need for improved medication adherence in chronic illness, few interventions have

successfully demonstrated increased long-term adherence to treatment (Haynes, Ackloo, Sahota, McDonald, & Yao, 2008).

Adherence in Multiple Sclerosis. 'Nonadherence' in MS can refer to declining recommended treatment at the outset, deviating from prescribed regimens, missing recommended doses, or prematurely terminating treatment against medical advice (Bruce & Lynch, 2011). Poor medication adherence is especially pervasive in MS, as approximately 30-50% of RRMS patients prematurely discontinue prescribed medication regimens (Cunningham, Gottberg, von Koch, & Hillbert, 2010; Reynolds, Stephen, Seaman, & Rajagopalan, 2010).

Previously, DMTs were limited to injectable medications (Wright, Yelland, Heathcote, Ng, & Wright, 2009) which was thought to be a primary factor associated poor adherence in MS (Bayas, 2013; Lugaresi, 2009; Mohr, Cox, Epstein, & Boudewyn, 2002). Wong et al. (2011) examined long-term adherence to injectable DMTs using a Canadian public dataset, and found that nearly half of the patients discontinued DMTs within 2 years of beginning treatment. Similarly, poor adherence due to injection-related factors is one of the most commonly cited reasons for nonadherence (Devonshire et al., 2011; Treadaway et al., 2009). Therefore, DMT adherence was expected to increase with the recent release of new oral medications (B. A. Cohen & Rieckmann, 2007; Gasperini & Ruggieri, 2011; Lipsy, 2010; Lorefice et al., 2015), and preliminary analysis revealed increased adherence to Gilenya (generic name fingolimod; a once daily pill) over injectable DMTs (Bergvall et al., 2014). More time is needed to assess long-term adherence to oral DMTs. It is worth noting, however, that patients with other chronic conditions that require oral medication administration commonly exhibit poor adherence. For example, up to 81% of patients prescribed antihypertensive treatments are nonadherent after one year (Van Wijk, Klungel, Heerdink, & de Boer, 2005), demonstrating the complexity of long-term adherence *despite* available oral treatments (Caro, Salas, Speckman, Raggio, & Jackson, 1999). Adherence is a multifaceted construct (J. M. Bruce, L. Hancock, P. Arnett, & S. Lynch, 2010; Pozzilli, Schweikert, Ecari, & Oentrich, 2011; Reynolds et al., 2010; Wong, Gomes, Mamdani, Manno, & O'Conner, 2011) that cannot be fully

explained by treatment modality alone, as problems with long-term adherence persist beyond method of delivery.

Barriers to Adherence in Chronic Disease. Despite medical and technological advances, medication adherence continues to pose challenges for both patients and providers (Menzin et al., 2013). Common barriers to treatment among those with chronic illnesses include perceived lack of efficacy (Gatwood et al., 2015), complex medication regimens (Choudhry et al., 2011; Saini et al., 2009), inconvenience, cost, and adverse side effects (Klauer & Zettl, 2008; Sabate, 2003). Concerns over treatment efficacy may result from a lack of immediately observable benefits. Instead of reducing current symptoms, long-term treatments for chronic conditions are designed to reduce the likelihood of future symptoms. For instance, hypertension medications offer no immediate relief, but instead are intended to reduce the risk of future vascular events. Thus, patients may conclude their treatment is ineffective because they feel no different than before (or may even feel worse due to side effects), resulting in the premature discontinuation of prescribed medications (Clerico, Barbero, Contessa, Ferrero, & Durelli, 2007; Rio et al., 2005; Tremlett & Oger, 2003).

Medication regimens with increased complexity are also associated with poor adherence in chronic disease (Choudhry et al., 2011; Saini et al., 2009), which suggests that simplifying medication schedules may improve adherence (Ingersoll & Cohen, 2008; Linnebur et al., 2014). However, problems with long-term adherence persist even after changes are made to simplify medication regimens (Nieuwlaat et al., 2014). The use of technology, such as smartphone alerts, alarms, and text-messages to prompt adherence are being explored. One study on adult diabetics found decreased adherence in both the intervention and control groups when text messages were used to prompt medication use; the authors proposed that perceived lack of treatment efficacy was the primary reason for these findings (Gatwood et al., 2015). Moreover, interventions that employ prompts may not increase medication adherence among patients who prematurely discontinue medication, as patients seldom report forgetfulness as a primary reason for premature discontinuation (McHorney & Spain, 2011).

Barriers to Adherence in Multiple Sclerosis. Barriers to adherence in MS often include the adverse side effects of DMTs, such as flu-like symptoms and injection-site reactions (Bayas & Rieckmann, 2000), which can interfere with daily activities and quality of life. Multiple longitudinal studies have found perceived lack of efficacy and side effects to be the primary reasons for discontinuation of prescribed treatments. In one study, nearly half of the sampled MS patients prematurely discontinued prescribed DMTs over the course of four years (Portaccio, Zipoli, Siracusa, Sorbi, & Amato, 2008), while another study reported approximately 75% of patients discontinued treatment (Bischoff, Schreiber, & Bergmann, 2012). Shinto et al. (2005) conducted a cross-sectional analysis of perceived benefit and satisfaction among treatments and providers of complementary and alternative medicine (CAM) as well as conventional therapies. Their results indicated that despite no significant difference in satisfaction between CAM providers and neurologists, patients who receive both CAM and traditional treatments perceived greater benefit from conventional therapies, reiterating the significance of perceived treatment efficacy (Shinto et al., 2005). Overly optimistic patients may also misunderstand treatment utility and become frustrated when anticipated outcomes (such as significant reductions in relapses or halted disease progression) do not occur, leading to premature discontinuation of DMTs (Mohr et al., 1996). Disease trajectory may also play a role in poor adherence, as patients with greater disease activity appear more adherent to medical appointments and DMTs than those with less active disease (J.M Bruce et al., 2010). Overall, notable barriers to adherence include medication side effects (Benito-Leon, Morales, & Rivera-Navarro, 2002; Janssens et al., 2003; Kes et al., 2013), perceived lack of social support (Mohr, Classen, & Barrera, 2004; Saunders, Caon, Smrtka, & Shoemaker, 2010), incongruent physician recommendations (Salter et al., 2014), low self-efficacy, and depressed mood (J. M. Bruce, L. M. Hancock, P. Arnett, & S. Lynch, 2010; Jongen et al., 2011).

Social Support

Psychosocial functioning, including social support, is also associated with treatment adherence (Klauer & Zettl, 2008). Social support has been identified as a key component for optimizing recovery and healthcare outcomes in chronic illness (S. Cohen, 1988; Fischer et al., 1999). This multidimensional

construct (Sherbourne & Stewart, 1991) is strongly associated with health-related quality of life (HRQL) (Fischer et al., 1999), emotional and physical recovery from illness (Heitzmann & Kaplan, 1988; Kaplan & Toshima, 1990; Tilden, 1985), medication adherence (Devonshire et al., 2011; Treadaway et al., 2009), and disease management (Kaplan & Toshima, 1990). Social support commonly occurs in group settings, which have been shown to aid in coping with chronic conditions such as MS (Bambara, Turner, Williams, & Haselkorn, 2014; Forman & Lincoln, 2010) by normalizing stressors associated with the disease (Forman & Lincoln, 2010), and providing a sense of group cohesiveness (Wakefield, Bickley, & Sani, 2013). Social support can also be provided on an individual basis, such as patient-provider relationships, which can promote shared decision-making, resulting in reduced healthcare costs and improved likelihood of treatment adherence (Oshima Lee & Emanuel, 2013). Therefore, providers may be able to significantly impact patients' healthcare experiences. Treadaway et al. (2009) examined factors that contribute to nonadherence to DMTs among 798 MS patients and found that both adherent and nonadherent patients identified their treatment provider as their strongest source of support. Another study examining treatment perceptions, DMT adherence, and quality of life found that approximately half of the patients reported wanting more time with their providers (Jérôme de Seze, Borgel, & Brudon, 2012).

Perceived Provider Support. Physician endorsement of treatments and confidence in DMT efficacy have also been identified as a primary factors for promoting DMT initiation and long-term treatment persistence (Cira Fraser, Hadjimichael, & Vollmer, 2003). Among 341 adherent and nonadherent RRMS patients, physician endorsement of Copaxone was a significant predictor of adherence (C. Fraser, Hadjimichael, & Vollmer, 2001). A separate study also found perceived provider support for the continued use of Copaxone to be a significant predictor of adherence among 199 progressive MS patients (Cira Fraser et al., 2003). Providers that promote DMT efficacy and encourage positive DMT experiences may decrease premature treatment discontinuation due to flu-like symptoms and injection-site reactions (Ross, 2008). This may also reassure patients who are skeptical of medications and the healthcare system (Ross, 2008; Schafheutle, 1998). Furthermore, perceived provider support may extend beyond face-to-face interactions. Factors such as provider availability through appointment

scheduling may also influence patients' feelings towards their providers (Organization, 2003; Salvo & Cannon-Breland, 2015; Touchette, 2010).

Burke and Dunbar-Jacob (1995) suggest that physician support influences adherence through providers' ability to communicate openly and without judgment, while conveying important disease and treatment-related information. Patient-centered approaches are commonly employed to strengthen patient-provider relationships where providers use techniques such as autonomy support to better understand patients' preferences and needs (Jackson, 2013; Remington, Rodriguez, Logan, Williamson, & Treadaway, 2013). This approach promotes mutual decision-making between patients and providers, (Aloia, Arnedt, Strand, Millman, & Borrelli, 2013; Caon, Saunders, Smrtka, Baxter, & Shoemaker, 2010; Falvo, 2010; Gance-Cleveland, 2007; Turner et al., 2014) which has been shown to increase the likelihood of patients' commitment to treatment (Oshima Lee & Emanuel, 2013). Moreover, collaborative and supportive patient-provider relationships can improve DMT adherence by collectively identifying and addressing barriers, devising solutions, and tracking progress (Turner et al., 2014; Von Korff, Gruman, Schaefer, Curry, & Wagner, 1997).

Unfortunately, patients with chronic conditions often face disease-related barriers that impede access to external social support opportunities (Heitzmann & Kaplan, 1988) such as challenges with mobility, fatigue, and incontinence (Zwibel, 2009). However, living with a chronic condition often requires frequent medical appointments, which allow for the development and perpetuation of social support through patient-provider relationships. Patient-centered approaches, such as autonomy support, have been shown to promote shared decision-making between patients and providers (Jackson, 2013; Remington et al., 2013). Ultimately, providers can influence adherence to treatment (L. Osterberg & T. Blaschke, 2005), expedite recovery, and improve healthcare outcomes (S. Cohen, 1988). The Global Adherence Project identified perceived support from neurologists as a significant factor in optimal DMT adherence (Jérôme de Seze et al., 2012; Devonshire et al., 2011). However, measures of adherence commonly focus on patients' commitment to treatment, as opposed to patient-provider relationships (Menzin et al., 2013) or perceived provider support. Despite extensive research on social support and

healthcare outcomes (Kulik & Mahler, 1989; R. Martin, Davis, Baron, Suls, & Blanchard, 1994), little is known about perceived provider support among RRMS patients who prematurely discontinue DMTs against medical advice. Patients who perceive less autonomy in their treatment options and report poor communication with providers may be more likely to prematurely discontinue DMTs against medical advice. To our knowledge, this is the first study to examine perceived provider autonomy support among nonadherent RRMS patients who have discontinued DMTs against medical advice.

Depression in Multiple Sclerosis

The WHO contends that depression is the leading cause of global disability and projects that depression will be the second greatest health concern by 2020 (Brundtland, 2001). Depression appears to be more prevalent in MS than most other neurologic conditions (Schiffer & Babigian, 1984; Schubert & Foliart, 1993) where more than 40% of MS patients utilize pharmacological treatment for depression (Patten, Williams, & Metz, 2008). Depression often adds to the existing challenges that MS patients face and is commonly associated with decreased quality of life (Amato et al., 2001; Janardhan & Bakshi, 2002; O'Connor, Lee, Ng, Narayana, & Wolinsky, 2001) as well as poor DMT adherence (J. M. Bruce, L. M. Hancock, P. Arnett, et al., 2010; D. C. Mohr et al., 1997; Mohr, Hart, Julian, & Tasch, 2007). One study examining patient characteristics and medication adherence among 8,067 patients with MS found that comorbid depression was associated with poorer adherence (Rolnick, Pawloski, Hedblom, Asche, & Bruzek, 2013). In a separate study, Bruce et al. (2010) found significant associations between emotional functioning and adherence when examining neuropsychiatric symptoms and long-term adherence in MS. Specifically, they found that patients with a mood or anxiety disorder were five times more likely to demonstrate poor ongoing adherence when compared to patients with no psychiatric diagnosis. Furthermore, patients who exhibited suboptimal adherence also reported more mood-related symptoms than adherent patients.

Patients with subclinical depression commonly exhibit poor DMT adherence indistinct from those with major depression (Sherbourne et al., 1994). Other studies examining depression and medication adherence in MS found that depressed patients experienced an increase in depressive symptoms within six

months of taking interferon beta (IFNß) and were more likely to struggle with DMT adherence compared to non-depressed patients (Mohr et al., 1996; D. C. Mohr, Ph.D. et al., 1997). However, results indicate that adherence improved in those who received psychotherapy or antidepressant treatment, suggesting early intervention for depression may improve DMT adherence (D. C. Mohr, Ph.D. et al., 1997). Due to the prevalence of mood disorders (specifically depression) in MS and their negative association with treatment adherence, prescribing physicians should regularly assess and treat psychiatric disorders to aid in improving DMT adherence (J. M. Bruce, L. M. Hancock, P. Arnett, et al., 2010; D. C. Mohr, Ph.D. et al., 1997; Pandya, Metz, & Patten, 2005). Nevertheless, despite known associations between depression and DMT adherence, little is known about the role depression plays among patients who prematurely discontinue DMTs against medical advice.

Clinical Disease-Related Characteristics

Despite unpredictable disease trajectory in RRMS (Kantarci & Wingerchuk, 2006), early DMT intervention is recommended to decrease the likelihood of relapses and slow disease progression (F. D. Lublin, Baier, & Cutter, 2003) by preventing repeated inflammation and demyelination in the CNS (Trapp et al., 1998) that can result in irreversible disability (Confavreux, Vukusic, Moreau, & Adeleine, 2000). Poor adherence within one year of initiating treatment can have significant adverse effects on patient outcomes (Tan, Cai, Agarwal, Stephenson, & Kamat, 2011). One study examining treatment outcomes found that patients who abstained from treatment for more than 90 days were twice as likely to experience a severe relapse compared to patients with shorter periods of nonadherence (Patti, 2010). Another longitudinal study found that increased exposure to IFN β-1a resulted in lower Expanded Disability Status Scale (EDSS) scores, fewer relapses, and decreased likelihood of developing secondary progressive MS compared to patients with less exposure to IFN β-1a treatment (Uitdehaag et al., 2011).

Although clinical trials have consistently demonstrated moderate levels of DMT efficacy (Inusah et al., 2010; Stellmann et al., 2012), there is no cure for MS, and disability commonly increases over time (F. D. Lublin et al., 2003). For example, up to 84% of patients with MS experience some form of autonomic dysfunction (J. de Seze et al., 2001; Vita et al., 1993) including incontinence,

thermoregulatory, or visual impairment (Racosta, Kimpinski, Morrow, & Kremenchutzky, 2015). Ambulatory problems, spasticity, and pain are also common (Crayton & Rossman, 2006; Poser, 1994). The progression of CNS damage over time can exacerbate physical and emotional difficulties (Marck et al., 2014), reduce quality of life (QOL) (McCabe & McKern, 2002), and impede disease management.

Despite the impact of physical symptoms on daily functioning, several adherence studies have found no significant association between disability, disease duration, and medication adherence (J. M. Bruce, L. M. Hancock, P. Arnett, et al., 2010; J. M. Bruce, L. M. Hancock, & S. G. Lynch, 2010). The relationship between disease duration, disability, and symptom activity among nonadherent RRMS patients who prematurely discontinue DMTs against medical advice is not well understood. Patients who experience less disease activity and longer disease duration may prematurely discontinue DMTs against medical advice because they feel they have a relatively benign presentation of the disease. Conversely, they may continue DMTs because they ascribe their benign course to successful treatment. Patients with greater symptom activity and physical disability may discontinue DMTs because they feel it is not working; conversely, they may be more likely to continue treatment because they are concerned about the aggressive nature of their disease course. More research is needed to understand the full extent of this relationship. Weak associations between disability, symptom activity, and disease duration may indicate more complex factors associated with nonadherence, beyond disease progression and the accumulation of physical disability. To our knowledge, this is the first study to examine disability, disease duration, symptom activity, and the extent to which providers believe their patients would benefit from DMTs among nonadherent patients who have prematurely discontinued DMTs against medical advice.

Summary

Poor medication adherence is prevalent in chronic illness and has universal implications for social, economic, and healthcare outcomes. Problems with treatment adherence are especially pervasive in MS, as up to 50% of patients prematurely discontinue DMTs despite the proven benefits of treatment. DMTs are associated with delayed disease progression, up to a 75% reduction in new brain lesions, and up to a 50% reduction in clinical exacerbations. However, DMTs do not ameliorate present symptoms,

which may cause patients to question the efficacy of their prescribed treatments. Combined with other barriers such as side effects, cost, and cognitive impairment, MS patients are forced to decide if the current sacrifice of adhering to DMTs is worth uncertain future benefit.

While several studies in the literature have examined self-reported adherence among MS patients who miss occasional doses or lack persistence, to our knowledge, this is the first study to examine social, emotional, and clinical disease-related characteristics among patients who have chosen to discontinue DMTs against medical advice. A better understanding of these factors may assist clinicians when discussing and prescribing DMTs to their patients.

Goals and Hypotheses

The current study investigated differences between adherent RRMS patients and nonadherent RRMS patients who have discontinued DMT against medical advice, accomplishing the following specific aims:

1. Examine differences in perceived social support between adherent and nonadherent RRMS patients. It was hypothesized that nonadherent MS patients would report receiving less provider support and less social support than adherent MS patients.
2. Examine the role that depressive symptoms plays in patients deciding to discontinue DMTs against medical advice. It was hypothesized that nonadherent patients would endorse more symptoms of depression and be more likely to meet criteria for major depressive episode than adherent patients.
3. Examine difference in clinical disease-related characteristics between DMT adherent and nonadherent RRMS patients. It was hypothesized that nonadherent MS patients would have greater disability than adherent patients.

CHAPTER 2

METHODOLOGY

Participants

One hundred twenty-nine participants with RRMS were recruited from three MS specialty clinics in the Midwest and Northeast in affiliation with the University of Kansas Medical Center, Saint Luke's Hospital, and the Kessler Foundation. Participants were also recruited by regional MS newsletters through the National MS Society and physician referral. Seventy-nine nonadherent subjects were paid $200 as compensation for their participation in a larger study examining treatment adherence in MS. Fifty adherent subjects were recruited for comparison and paid $25 for participation in this study. Criteria for inclusion in the larger study included: (a) diagnosis of RRMS by a board-certified neurologist based on established guidelines (Polman et al., 2005); (b) physician recommendation to take DMT; (c) premature discontinuation of prescribed DMTs; (d) no severe sensory, motor, physical, or neurological impairment that would make participation in the study insurmountable; (e) no history of nervous system disorder other than MS; (f) at least 18 years of age; and (g) English-speaking. Inclusion criteria for the current study was indistinguishable from that of the nonadherent study, except adherent participants were required to have taken at least 80% of prescribed DMT doses over the previous eight weeks. Previous research shows that although self-reported DMT adherence often overestimated, a single self-report measure of medication adherence in MS is highly correlate with objective measures of adherence (J.M Bruce et al., 2010). Therefore, the current study used a validated self-report question that asked participants the number of doses they had missed in the preceding 2 months. Consistent with our previous research, adherent patients were required to report a minimum of 80% DMT adherence for the two months prior to enrollment in the current study. All subjects were rated based on Kurtzke's Expanded Disability Status Scale (Kurtzke, 1983) by a board-certified neurologist or licensed neurology nurse practitioner.

Procedure

The investigation was based on data collected at baseline from a study examining a telephone-based treatment intervention for medication adherence in a sample of nonadherent RRMS patients. This study also included data collected from adherent RRMS patients for comparison. Once accepted into the study, both adherent and nonadherent subjects completed the same questionnaires, battery of neuropsychiatric tests, and psychiatric interviews. All procedures were approved by the institutional review boards at the University of Missouri-Kansas City, the University of Kansas Medical Center, Saint Luke's Hospital, and the Kessler Foundation. Written informed consent was obtained from all participants prior to study enrollment.

Measures

Perceived Social Support

MOS Modified Social Support Survey (MSSS)(Sullivan, Edgley, & Dehoux, 1990). The MSSS is frequently used in MS research to assess perceived social support. The measure begins by asking, "How often is someone available…" and includes example items such as, "to take you to the doctor if you need to go?" and "to hug you?" Participants were asked to rate perceived social support, using a five-point scale, where higher scores indicated greater perceived social support. The five-item version that most strongly correlates with the full-length 18-item version was used in the sample (Ritvo et al., 1997). Highly correlated with a measure of loneliness and companionship, but not measures of vision and incontinence, this measure shows good convergent and discriminant validity and has a Cronbach's alpha of 0.88 (Sherbourne & Stewart, 1991).

Health Care Climate Questionnaire (HCCQ)(G. C. Williams & Deci, 2001). The HCCQ is used in adherence research to assess patients perceived autonomy support from health care providers. In this sample, participants were asked to rate perceived support from their healthcare provider regarding MS medication. Patients responded to six-items, using a Likert-type scale ranging from 1 (*not at all true*) to 7 (*very true*), where higher scores indicated greater perceived autonomy support from their MS health care provider. This six-item questionnaire has been shown to be a valid and reliable measure (alpha = 0.96) (Carroll et al., 2013; G. C. Williams, Grow, Freedman, Ryan, & Deci, 1996).

Depression

Mini International Neuropsychiatric Interview (MINI): Depression module (Sheehan et al., 1998). The MINI is a semi-structured psychiatric interview that conforms to DSM-IV-TR standards for diagnosing mental disorders and has been previously used for clinical diagnoses in MS (Arnett, Barwick, & Beeney, 2008; Sheehan et al., 1998).

Mental Health Inventory (MHI)(Veit & Ware, 1983). The MHI is frequently used in MS research to assess various aspects of self-reported mental health such as anxiety, depression, behavioral control, positive affect, and general distress. The full-length, 18 item version was used in this sample. Participants were asked to rate their emotions over the past four weeks, using a six-point scale, where higher scores indicated better mental health. The MHI is a valid and reliable measure that is highly correlated with additional mental health assessments, and a Cronbach's alpha of 0.93 (Sherbourne, Hays, Ordway, DiMatteo, & Kravitz, 1992; Veit & Ware, 1983).

Clinical Disease-Related Characteristics

Expanded Disability Status Scale (*EDSS*)(*Kurtzke, 1983*). The EDSS is a measure of MS disease progression and neurological impairment. Eight functional systems are examined and combined for a composite score ranging from zero (normal neurologic exam) to 10 (death due to MS). The EDSS is frequently used in both clinical practice and research in order to quantify the disability associated with MS. Each patient was rated on the EDSS by a board-certified neurologist. Higher scores indicate more overall disability.

Factors of Nonadherence

Multiple Sclerosis-Treatment Adherence Questionnaire (MS-TAQ)(Wicks, Massagli, Kulkarni, & Dastani, 2011). The MS-TAQ ($\alpha = 0.81$) is frequently used in MS research to assess the extent to which common barriers of adherence influence patients' decisions to take DMTs. The measure begins by asking, "How important were the following factors in deciding not to take your medications?" and includes example items such as, "memory problems," "side effects of medication," and "dis-satisfaction with medication." Adherent patients completed the same questionnaire, but responded to the instruction, "To

what extent does each of the following factors make it difficult for you to adhere to your MS medication?" Participants rated how important each factor influenced their decision not to take DMTs on a four-point scale, where higher scores indicated the barriers as extremely important. This measure was included for post hoc analyses to elucidate the role of barriers to adherence and perceived provider autonomy support.

Statistical Analysis

Proposed Analytic Plan. For the present study, 50 adherent patients were recruited and compared to 79 nonadherent patients who completed the same test battery as part of a larger study examining treatment adherence outcomes. Based on previous research examining predictors of nonadherence in MS, we had more than sufficient power (>0.80) to detect small to moderate effects (d = 0.44), with $p \leq 0.05$ indicating statistical significance. Group differences for demographic and clinical variables, such as disease duration were assessed using *t*-tests and chi-squared analysis; significant variables were included as covariates in subsequent analyses.

Aim 1: It was hypothesized that nonadherent MS patients would endorse less perceived provider support and less social support than adherent MS patients. Analysis of covariance (ANCOVA) was used to examine group differences on each measure of social support, controlling for education, disease duration, disability, and whether or not patients had a current MS healthcare provider.

Aim 2: It was hypothesized that nonadherent patients would endorse more symptoms of depression and be more likely meet criteria for major depressive episode than adherent patients. Chi-Square analysis was used to examine between group differences in DMS-IV-TR mood diagnoses (depression). Group differences on the MHI were examined using analysis of covariance (ANCOVA), controlling for education, disease duration, disability, and whether or not patients had a current MS healthcare provider.

Aim 3: It was hypothesized that nonadherent patients would have more disability than adherent patients. Group differences on disability and symptom activity were examined using analysis of covariance (ANCOVA), controlling for education, disease duration, and whether or not patients had a current MS healthcare provider.

CHAPTER 3

RESULTS

Descriptive Data

The sample included 129 RRMS patients (50 adherent, 79 nonadherent). Among adherent participants, 38 were women (76%) with an average age of 43.94 ± 9.61 years. The majority of adherent patients had completed some college (20%) or graduated with a Bachelor's or Master's degree (44%). Adherent subjects were primarily Caucasian (84%, n=42), followed by African American (12%, n=6), Hispanic/Latino (2%, n=1), and Asian or Pacific Islander (2%, n=1). The average diagnosis duration in the adherent group was 7.10 ± 6.38 years, with an average EDSS score of 2.35 ± 1.26. Patients reported current use of the following disease modifying therapies: Copaxone (66%), Avonex (20%), Betaseron (20%), Rebif (12%), Tysabri (6%), Gilenya (14%), Tecfidera (20%), Aubagio (10%), Extavia (4%). The majority of adherent patients reported a minimum of 90% DMT adherence over eight weeks (96%, n=48) prior to study participation, while 4% (n=2) reported a minimum of 80% adherence. Nearly all adherent participants reported currently seeing a MS treatment provider on a regular basis (98%).

The nonadherent sample included 79 subjects, who were predominantly female (88.6%, n=70) with an average age of 45.34 ± 10.78 years. No significant differences were found between adherent and nonadherent groups in terms of age, $t(127) = 0.749$, $p > 0.05$ or gender, $\chi^2(1, N = 129) = 3.57$, $p > 0.05$. The majority of nonadherent participants completed at least some college (43%) or graduated with a Bachelor's or Master's degree (36.7%) and identified as Caucasian (81%, n=64), African American (19%, $n = 15$), or Native American (1.3%, n=1). Chi-square analyses revealed that adherent patients had more education than the nonadherent group, $\chi^2(5, N = 129) = 11.74$, $p = 0.038$. Ethnicity was not significantly different between the groups, $\chi^2(3, N = 129) = 4.11$, $p > 0.05$. Average diagnosis duration in the nonadherent group was 11.14 ± 8.11 years, with an average EDSS score of 3.00 ± 1.34. *T*-tests revealed that the nonadherent group had longer disease duration, $t(127) = 2.98$, $p < 0.05$ and greater disability, $t(127) = 2.76$, $p < 0.05$, than the adherent group. Patients reported previous use of the following disease modifying therapies: Copaxone (70.9%), Avonex (43%), Betaseron (29.1%), Novantrone (1.3%), Rebif

(26.5%), Gilenya (3.7%), Tysabri (6.3%), and Tecfidera (1.2%). Significantly fewer nonadherent patients reported currently seeing a MS treatment provider on a regular basis than adherent patients, $\square^2(1, N = 129) = 13.08$, $p < .001$. Significant demographic and clinical variables will be included as covariates in subsequent analyses. See Table 1 for descriptive characteristics.

Table 1

Descriptive characteristics of the sample.

	Adherent Subjects *n* (%) or Mean (SD)	**Nonadherent Subjects** *n* (%) or Mean (SD)
Gender		
Female	38 (76%)	70 (88.6%)
Male	12 (24%)	9 (11.3%)
Race		
Caucasian	42 (84%)	64 (81%)
African American	6 (12%)	15 (19%)
Hispanic/Latino	1 (2%)	…
Other	1 (2%)	1 (1.3%)
Age (years)	43.94 ± 9.61	45.34 ± 10.78
Education		
Less than high school graduate	1 (2%)	3 (3.7%)
High school graduate	8 (16%)	4 (5%)
Some college	10 (20%)	34 (43%)
Graduated 2-year college with Associates Degree	6 (12%)	8 (10.1%)
Graduated 4-year college with Bachelor's or Master's Degree	22 (44%)	29 (36.7%)
Doctoral/Professional degree or other	3 (6%)	1 (1.2%)
Duration of Diagnosis (years)	7.55 ± 6.37	11.62 ± 8.11
EDSS	2.35 ± 1.26	3.00 ± 1.34

DMT		
Copaxone	33 (66%)	56 (70.9%)
Avonex	10 (20%)	34 (43%)
Betaseron	10 (20%)	23 (29.1%)
Novantrone	…	1 (1.3%)
Rebif	6 (12%)	21 (26.5%)
Tysabri	3 (6%)	5 (6.3%)
Gilenya	7 (14%)	3 (3.7%)
Aubagio	5 (10%)	…
Extavia	2 (4%)	…
Tecfidera	10 (20%)	1 (1.3%)
Current MS healthcare provider	49 (98%)	59 (74.6)
DMT adherence of 90%	48 (96%)	…

Abbreviations: EDSS = Expanded Disability Status Scale; DMT = Disease Modifying Treatment

Adherence Results

Social Support and DMT Adherence. Differences between adherent and nonadherent RRMS patients on the self-report measures of social support and perceived autonomy support from provider were examined using ANCOVA, controlling for education, disease duration, EDSS, and current MS healthcare provider. Adherent subjects reported greater perceived autonomy support from their providers than nonadherent participants on the HCCQ, $F(1, 124) = 28.170$, $p < 0.001$, partial $\eta^2 = .185$. There were no significant differences in social support on the MSSS between adherent and nonadherent groups, $F(1, 124) = 1.525$, $p > 0.05$, partial $\eta^2 = 0.012$.

Depression and DMT Adherence. Adherent and nonadherent RRMS patients were compared on a self-report measure of depressive symptoms and a diagnostic interview instrument for clinical depression. No significant differences were found on the depression subscale of the MHI between adherent and nonadherent groups ($F(1, 124) = 1.001$, $p > 0.05$, partial $\eta^2 = 0.009$) controlling for education, disease duration, EDSS, and current MS healthcare provider or on the MINI Depression Module ($\chi^2(1, N = 129) = .288$, $p > 0.05$).

Disability and DMT Adherence. Differences between adherent and nonadherent groups on a clinical diagnostic instrument of disease progression and neurological impairment were examined using the EDSS. Controlling for education, disease duration, and current MS healthcare provider, nonadherent RRMS patients had more disability than adherent patients, $F(1, 124) = 4.251$, $p < 0.05$, partial $\eta^2 = 0.033$. Group differences are shown in Tables 2 and 3.

Table 2

Comparison of perceived social support, mental health, disability measures between adherent and nonadherent RRMS subjects.

Measure	Adherent RRMS Mean *(SD)*	Nonadherent RRMS Mean *(SD)*	*F*(df)	*p*
MSSS	77.90 *(24.49)*	71.39 *(22.61)*	1.52 (1, 124)	.232
HCCQ	6.16 *(0.92)*	4.81 *(1.74)*	28.17 (1, 124)	<.001
MHI Depression Subscale	74.20 *(21.69)*	70.63 *(25.61)*	1.00 (1, 124)	.319
EDSS	2.35 *(1.26)*	3.00 *(1.34)*	4.25 (1, 125)	.041

Abbreviations: MSSS = Modified Social Support Survey; HCCQ = Heal Care Climate Questionnaire; MHI = Mental Health Inventory; EDSS = Expanded Disability Status Scale

Table 3

Chi-square Test for Clinical Depression by DMT Adherence.

Major Depressive Episode, Current	Adherent RRMS Mean *(SD)*	Nonadherent RRMS Mean *(SD)*	χ^2 (df, *N*)	*p*
Yes	10	19		
			.288 (1, 129)	.591
No	40	60		

Exploratory Analysis. DMT side effects are one of the most commonly reported reasons for premature discontinuation (Bayas & Rieckmann, 2000; Benito-Leon et al., 2002; Bischoff et al., 2012; Heesen et al., 2014; Janssens et al., 2003; Portaccio et al., 2008). Therefore, we examined the difference between adherent and nonadherent RRMS patients on a self-report measure stating, "Why did you stop taking each medication (please list and describe if applicable)?" Responses were coded as dichotomous variables based on patients reporting "side effects" or listing specific side effects as their reason for discontinuing each DMT. Chi-square analysis revealed that nonadherent patients reported side effects as a reason for discontinuing DMTs significantly more often than adherent patients, $\chi^2(1, N = 129) = 15.10$, $p < 0.001$. We also examined a self-report measure of barriers to adherence that assessed the extent to which barriers influenced patients' decisions to adhere to DMTs, The Multiple Sclerosis Treatment Adherence Questionnaire (MSTAQ). Controlling for education, disease duration, EDSS, and current MS healthcare provider, ANCOVA analysis revealed that nonadherent participants placed significantly more value on the extent to which barriers influenced DMT adherence than adherent participants, ($F(1, 123) = 39.79$, $p < 0.001$, partial $\eta^2 = 0.240$). Group differences are shown in Tables 4 and 5.

Table 4

Chi-square Test for Side Effects as a Reason for Discontinuing DMTs.

Side Effects as a Reason for Discontinuing DMTs	Adherent RRMS Mean *(SD)*	Nonadherent RRMS Mean *(SD)*	χ^2 (df, *N*)	*p*
Yes	21	60	15.10 (1, 129)	<.001
No	29	19		

Table 5

Comparison of the extent to which common barriers influence DMT adherence between adherent and nonadherent RRMS subjects.

Measure	Adherent RRMS Mean *(SD)*	Nonadherent RRMS Mean *(SD)*	*F*(df)	*p*
MSTAQ	8.52 *(8.13)*	17.21 *(7.17)*	38.79 (1, 123)	<.001

Abbreviations: MSTAQ = Multiple Sclerosis Treatment Adherence Questionnaire

Social Support and DMT Adherence Controlling for Side Effects. The prevalence of side effects and extent to which DMT side effects influence patients' decision to adhere to medication differs between adherent and nonadherent groups. To determine if perceived autonomy support from provider (as measured by the HCCQ) remained significant, an ANCOVA was performed controlling for education, disease duration, EDSS, current MS healthcare provider, MSTAQ, and prevalence of side effects. Even when controlling for these variables, adherent patients still perceived more autonomy support from their provider than nonadherent patients, ($F(1, 121) = 9.61$, $p = 0.002$, partial $\eta^2 = 0.074$).

Differences in the Sample Based on Provider. Nonadherent patients were recruited from the community and three MS outpatient clinics, but all adherent patients were recruited from the same clinic and were under the care of the same healthcare provider. To determine if perceived provider autonomy support was significantly different between adherent and nonadherent patients recruited from the same clinic, an ANCOVA was performed controlling for education, disease duration, EDSS. Even when comparing adherent and nonadherent patients from the same clinic, adherent patients continued to perceived more provider autonomy support than nonadherent patients, ($F(1, 57) = 12.63$, $p = 0.001$, partial $\eta^2 = 0.178$), indicating that these differences remain even when patients have the same provider.

CHAPTER 4

DISCUSSION

The demands associated with long-term care of chronic conditions may impact patients' ability to continuously adhere to medication regimens (L. Osterberg & T. Blaschke, 2005; Saini et al., 2009; Sokol et al., 2005). Poor medication adherence is one of the most prevalent and costly problems in public health (Klauer & Zettl, 2008; Zullig et al., 2015), as nearly half of all patients with chronic conditions prematurely discontinue prescribed treatments (Ferrari et al., 2013; Harrison et al., 2013; Petri et al., 1991; Sabate, 2003). Despite efforts to improve adherence by increasing accessibility to healthcare services and medications (Berger et al., 2005), minimal long-term improvements to medication adherence have been observed (Haynes et al., 2008).

Adherence is conceptually complex and not fully understood, as many factors are thought to play a role in patients' decisions to adhere to medication. Common barriers to treatment among patients with chronic conditions include lack of perceived efficacy (Gatwood et al., 2015), complex treatment regimens (Choudhry et al., 2011; Saini et al., 2009), inconvenience, cost, and adverse side effects (Klauer & Zettl, 2008; Sabate, 2003). One primary reason patients may question the value of their treatment is a lack of observable benefit, such as symptom reduction (Clerico et al., 2007; Rio et al., 2005; Tremlett & Oger, 2003). For example, hypertension medication reduces the risk of future vascular events, but offers no immediate relief. Therefore, patients feel no different when adhering to their hypertension medication, leading them to believe their treatment is unhelpful and ultimately discontinuing these medications prematurely (Clerico et al., 2007; Rio et al., 2005; Tremlett & Oger, 2003). This effect has also been observed in other chronic conditions, such as diabetes (Gatwood et al., 2015) and MS (Bischoff et al., 2012; Portaccio et al., 2008).

Poor medication adherence is especially problematic in MS, as up to 50% of RRMS patients prematurely discontinue DMTs (Cunningham et al., 2010; Reynolds et al., 2010). Without a cure for MS, early DMT intervention has been shown to reduce relapses and slow the rate of future decline among RRMS patients (Freedman et al., 2013; Gold et al., 2010). Historically, DMTs were limited to

intramuscular or subcutaneous injections (Wright et al., 2009), but DMTs are now offered in oral capsules and intravenous infusions. Similar to hypertension medications, DMTs are preventive treatments that do not ameliorate current symptoms, and often cause undesirable side effects (Minen & Karceski, 2011). Additionally, DMT adherence does not guarantee future benefit because treatment outcomes vary, which may cause patients to question the efficacy of their treatment (O'Rourke & Hutchinson, 2005; Rio et al., 2005).

In addition to perceived lack of treatment efficacy, known barriers to DMT adherence include medication side effects (Benito-Leon et al., 2002; Janssens et al., 2003; Kes et al., 2013), perceived lack of social support (Mohr et al., 2004; Saunders et al., 2010), incongruent physician recommendations (Salter et al., 2014), low self-efficacy, and depressed mood (J. M. Bruce, L. M. Hancock, P. Arnett, et al., 2010; Jongen et al., 2011). Another factor may involve overly optimistic patients who misunderstand the utility of their treatment and are overconfident in anticipated results, subsequently leading to disappointment and premature DMT discontinuation (Mohr et al., 1996). Disease trajectory may also impact adherence, as patients with less active disease attend fewer medical appointments and demonstrate poorer DMT adherence than those with a more active disease course (J.M Bruce et al., 2010).

Adherence is difficult to study due to a lack of consensus in one standardized definition. 'Nonadherence' is characterized in many forms, including declining recommended treatment, deviating from prescribed regimens, missing recommended doses, or prematurely terminating treatment against medical advice (Bruce & Lynch, 2011). Most studies examine nonadherence in the context of missing doses or discontinued treatment. One published study found that patients who discontinue medications against their providers' advice may magnify treatment risks and minimize treatment benefits (J. M. Bruce et al., 2015). No other study has examined factors associated with premature DMT discontinuation among RRMS patients who stopped treatment against medical advice. Therefore, the current study sought to examine factors associated with this form of nonadherence: DMT discontinuation against medical advice. To our knowledge, this is the first study to examine perceived provider autonomy support, depression, disability, and the extent to which providers believe their patients would benefit from DMTs among

nonadherent patients who prematurely discontinued DMTs against medical advice. It is hoped that a better understanding of the complexities associated with nonadherence will aid interventions aimed at improving long-term adherence.

Summary of Findings

The current study sought to evaluate perceived social and autonomy support, depression, and clinical disease-related characteristics between adherent and nonadherent RRMS patients who discontinued treatment against medical advice. Education, disease duration, and EDSS were controlled for when examining perceived social support and depression, while education and disease duration were controlled for when evaluating EDSS.

Perceived Social Support. The first hypothesis predicted that nonadherent RRMS patients would report less social support than adherent MS patients. The current study found no significant differences between adherent and nonadherent groups on perceived social support. The association between social support and medication adherence is not fully understood, as perceived lack of social support is often, but not always, identified as a factor associated with nonadherence (Mohr et al., 2004; Saunders et al., 2010). Social support theories often emphasize the role of social support in positive health-behaviors (S. Cohen, 1988; Kouvonen et al., 2012; Shiovitz-Ezra & Litwin, 2012), including medication adherence (Petrova, Garcia-Retamero, & Catena, 2015). Social support in group settings has been shown to aid in coping with chronic conditions (Bambara et al., 2014; Forman & Lincoln, 2010) by normalizing the disease (Forman & Lincoln, 2010), and providing group belongingness (Wakefield et al., 2013). Social support has also been found to promote recovery and healthcare outcomes in chronic illness (S. Cohen, 1988; Fischer et al., 1999), given its link to medication adherence (Devonshire et al., 2011; Treadaway et al., 2009) and disease management (Kaplan & Toshima, 1990). One study examining antihypertension medication adherence among African American patients found that greater social support was associated with better adherence (Grant et al., 2015). Conversely, a randomized controlled trial on long-term adherence in diabetes found that two social support intervention groups did not differ in adherence from the control group over a three month period (Reese et al., 2015). However, Treadaway et

al. (2009) examined nonadherence among MS patients and found that both adherent and nonadherent patients identified their treatment provider as their strongest source of support, indicating that providers can lend social support to patients with techniques such as shared decision-making that may influence treatment adherence (Oshima Lee & Emanuel, 2013). This finding suggests that treatment providers may be able to significantly impact patients' willingness to adhere. Indeed, the Global Adherence Project identified perceived support from neurologists as a significant factor in optimal DMT adherence (Jérôme de Seze et al., 2012; Devonshire et al., 2011).

Perceived Provider Support. The first hypothesis also predicted that nonadherent RRMS patients would report less perceived provider autonomy support than adherent MS patients. Consistent with this hypothesis, adherent RRMS patients reported significantly more perceived autonomy support from their MS treatment provider than nonadherent patients. This finding is consistent with other studies on perceived autonomy support and medication adherence among patients with chronic conditions, where the role of patient-provider relationships emphasize effective communication (L. R. Martin, DiMatteo, & Lepper, 2001; O'Malley, Forrest, & Mandelblatt, 2002) and perceived provider support (Devonshire et al., 2011) beyond general social support. Patient autonomy is a primary factor in medical decision-making and can be used to promote adherence (Heesen, Köpke, Solari, Geiger, & Kasper, 2013), emphasizing the significance of active patient participation in shared decision-making over treatment decisions (Kasper, Hoffmann, Heesen, Köpke, & Geiger, 2012). Techniques such as autonomy support can improve patient-provider relationships, which allows the provider to better understand patients' preferences and needs (Jackson, 2013; Remington et al., 2013), and promotes mutual decision-making (Aloia et al., 2013; Caon et al., 2010; Falvo, 2010; Gance-Cleveland, 2007; Turner et al., 2014). Patient-centered approaches, such as autonomy support and shared decision-making, can influence adherence to treatment (L. Osterberg & T. Blaschke, 2005). One recent randomized clinical trial designed to improve adherence combined Motivational Interviewing and Cognitive Behavioral Therapy (MI-CBT). MI-CBT emphasizes a supportive clinical environment that fosters patient autonomy in medical decision-making. Results demonstrated that this approach significantly increased treatment adherence among patients who had

previously discontinued DMTs against medical advice (J. Bruce et al., 2015), again pointing toward the importance of a supportive and empowering clinical environment.

Consistent with our findings on perceived provider autonomy support, one study on decreasing diabetes health risks found that increased perceived autonomy support from healthcare providers was associated with more adherent self-regulated medication use (Geoffrey C. Williams et al., 2009). Another study on autonomous regulation and long-term adherence found that perceived autonomy support was directly associated with increased medication adherence and increased autonomous regulation among diabetic patients (G. C. Williams, Rodin, Ryan, Grolnick, & Deci, 1998). Furthermore, one study examining patient views on medication adherence after a cardiac event suggested that an increase in providers' willingness to elicit communication and empathize with patient views on treatments significantly improved adherence (Lambert-Kerzner et al., 2015). However, physician overestimation of DMT adherence may influence their evaluation of treatment efficacy, resulting in unnecessary increases in treatment doses. This suggests that improved communication between patients and providers would likely aid in treatment decision-making, improved evaluations of treatment efficacy, and medication adherence (Riñon, Buch, Holley, & Verdun, 2011). Taken together, these results emphasize the significant role of patient-provider relationships and adherence. Overall, our findings are consistent with the literature on patient-provider relationships which emphasize the role of the healthcare provider in patients' decision to adhere to their DMTs.

Depression and Medication Adherence. The second hypothesis predicted that nonadherent RRMS patients would endorse more symptoms of depression and be more likely to meet criteria for major depressive disorder than adherent patients. Our results did not support this hypothesis. The depression subscale on the self-report measure of mental health (on the MHI) revealed no significant difference between the adherent and nonadherent groups. Furthermore, neither group differed in the prevalence of DSM-IV major depression.

Depression is more prevalent in MS than other neurologic conditions (Schiffer & Babigian, 1984; Schubert & Foliart, 1993) and may affect patients' ability to adhere to treatment (J. M. Bruce, L. M.

Hancock, P. Arnett, et al., 2010; D. C. Mohr et al., 1997; Mohr et al., 2007). Previous research has shown that MS patients who report more mood disturbance also have poorer adherence (Rolnick et al., 2013) (J. M. Bruce, L. Hancock, & S. Lynch, 2010). Comorbid depression diagnoses, as well as subclinical depression, have also been shown to impede medication adherence in MS (J. M. Bruce, L. M. Hancock, P. Arnett, et al., 2010; Treadaway et al., 2009). In contrast, one study examining DMT use in MS initially found no significant difference in adherence among patients who were treated and not treated for clinical depression (Tarrants, Oleen-Burkey, Castelli-Haley, & Lage, 2011). Despite previous literature showing an association between depression and poor adherence, including the treatment of depression leading to improved adherence, our findings do not support any significant differences in depression between adherent and nonadherent patients. As previously discussed, nonadherence varies by definition, resulting in many types of nonadherence in the research literature. The aforementioned studies typically examined patients who demonstrated poor or suboptimal adherence, such as taking fewer DMT doses than what was recommended or prescribed. However, the current study limited enrollment to nonadherent patients who prematurely discontinued DMTs against medical advice, suggesting these patients, who actively chose to abstain from DMT treatment despite physician recommendation, may differ from nonadherent patient samples in other studies, and therefore may require a tailored intervention or more patient-centered approach to improve adherence.

Disability and Medication Adherence. The third hypothesis predicted that nonadherent RRMS patients would exhibit more disability than adherent patients. Our results supported this hypothesis. Nonadherent patients demonstrated significantly more disability than adherent patients on the EDSS. This finding supports prior research showing that poor DMT adherence can have significant adverse effects on patient outcomes (Tan et al., 2011), even among patients with short periods or lapses of nonadherence (Patti, 2010). Early DMT intervention is recommended to decrease the likelihood of relapses and slow disease progression (F. D. Lublin et al., 2003) by preventing recurring lesions in the CNS (Trapp et al., 1998) that can result in irreversible disability (Confavreux et al., 2000). Therefore, one possible explanation for the current finding is that nonadherent RRMS patients who prematurely discontinued

DMTs against medical advice have greater disability than adherent patients as a result of untimely termination of MS treatment.

However, this finding is not consistent with other studies that revealed no significant association between disability, disease duration, and medication adherence (J. M. Bruce, L. M. Hancock, P. Arnett, et al., 2010; J. M. Bruce, L. M. Hancock, & S. G. Lynch, 2010). One notable difference between the previous and current studies is that the previous research defined nonadherence as taking fewer than 80% of prescribed doses. No prior studies have examined the relationship between disability and DMT adherence among adherent and nonadherent RRMS patients who prematurely discontinued DMTs against medical advice. One possible explanation for poor adherence among MS patients with more disease activity is a lack of awareness of increasing disability; consequently, they may feel that they are doing fine and do not require medication. Another possible reason may be that increasing symptomatology does not motivate patients to adhere to DMTs or perhaps greater physical disability causes a lack of perceived medication efficacy, resulting in premature DMT discontinuation. Future research is needed to explore the full extent of this relationship, as more complex factors, beyond the risk of greater disability, may influence patients' willingness to adhere.

Limitations

This study has a number of potential limitations. First, adherence is inconsistently defined in the scientific literature. Previous research on injectable DMTs commonly defined missing one or more doses over a specified period of time as nonadherent (Steinberg, Faris, Chang, Chan, & Tankersley, 2010; Treadaway et al., 2009). However, missing one dose may not be clinically relevant (Zettl, Bauer-Steinhusen, Glaser, Hechenbichler, & Limmroth, 2013) because the number of doses needed to achieve therapeutic effectiveness can vary by medication and patient characteristics. As a result, no gold standard threshold for DMT adherence exists. Consequently, consistent with other studies in MS, the current study required a minimum of 80% self-reported adherence to prescribed DMTs for two months prior to study enrollment to qualify as an adherent participant. Self-reported adherence has been shown to be highly correlated with objective measures of adherence in MS (J.M Bruce et al., 2010). Only two participants

reported a minimum of 80% adherence, the rest of the adherent sample reported more than 90% DMT adherence.

Second, patient familiarity with treatment options was not assessed. This may inform patients' willingness to adhere, as a better understanding of MS, disease progression, DMTs, and available treatment options may influence patients' willingness to adhere. One study found that fear of relapses and future disability were primary motivators for DMT adherence (Turner, Kivlahan, Sloan, & Haselkorn, 2007). Education on treatment options, expectations, and MS is considered a helpful strategy in sustaining adherence (Costello, Kennedy, & Scanzillo, 2008). Increased patient knowledge of DMT options may promote patient-provider relationships, shared decision-making, commitment to treatment and improved adherence.

Finally, the current study was limited to a cross-sectional design. The inability to randomize participants to groups restricted our understanding of causal ordering such as the sequential association between disability and adherence.

Conclusion

Poor patient-provider relationships are associated with nonadherence (L. Osterberg & T. Blaschke, 2005) to the extent that perceived physician support is a significant predictor of adherence (C. Fraser et al., 2001). Open communication (Burke & Dunbar-Jacob, 1995) and patient autonomy (Jackson, 2013; Remington et al., 2013) can improve shared decision-making between patients and providers (Aloia et al., 2013; Caon et al., 2010; Falvo, 2010; Gance-Cleveland, 2007; Turner et al., 2014), increasing the likelihood of commitment to treatment (Oshima Lee & Emanuel, 2013). The results of the current study suggest that RRMS patients who discontinue DMTs against medical advice report less perceived autonomy support from their physician. This finding is independent of side effects, whether patients are actively seeing an MS treatment provider, the extent to which barriers to adherence influence patients' decision to take DMTs, education, disability, and disease duration. When taken in context with other research, including a recent clinical trial using Motivational Interviewing to improve adherence (J. Bruce et al., 2015) and the use of shared decision-making to increase adherence (Heesen et al., 2013), the

current findings emphasize the importance of strong patient-provider relationships and autonomy support for optimizing DMT adherence. Results may inform future interventions aimed at improving treatment adherence amongst patients that demonstrate poor adherence, as well as those who prematurely discontinue DMTs against medical advice. Future research should elucidate the role of perceived provider autonomy support among nonadherent patients and explore interventions aimed at improving provider autonomy support.

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