

POLYPHARMACY IN PATIENTS WITH MULTIPLE SCLEROSIS:
EFFECTS ON FATIGUE, PERCEIVED COGNITION, AND
OBJECTIVE COGNITIVE PERFORMANCE

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ABSTRACT

OBJECTIVE: Many individuals with multiple sclerosis (MS) take multiple medications on a regular basis, also referred to as polypharmacy. In other patient populations, polypharmacy has been associated with fatigue and cognitive dysfunction. However, no study has examined polypharmacy in MS. We explored the association between polypharmacy, fatigue, and cognition in a group of participants with MS.

METHODS: Data for this study were collected as part of a larger investigation examining medication adherence in MS. The sample included 86 patients with MS and 20 healthy controls. We assessed objective cognitive functioning, self-reported cognition, and self-reported fatigue. In addition, a list of patients' medications was obtained at the time of testing. Polypharmacy was classified using a cutoff of 5 or more daily medications.

RESULTS: Approximately 33% of the MS sample had polypharmacy. After controlling for age, disease duration, and disability, MS patients with polypharmacy reported more memory problems, processing speed difficulties, and fatigue than MS patients without polypharmacy, $F(1, 79) = 13.09, p = .001$ and $F(1, 79) = 7.33, p < .01$, $F(1, 79) = 10.45, p < .01$, respectively. MS patients with polypharmacy also exhibited worse prospective memory performance than patients without polypharmacy, $F(1, 77) = 12.67, p = .001$.

CONCLUSIONS: This is the first study to examine the association between fatigue, cognition, and polypharmacy in MS patients. Results suggest that researchers should account for polypharmacy and medication effects when conducting studies examining fatigue and cognition in MS. Similarly, clinicians and patients should carefully weigh the costs and benefits of prescribing multiple medications, as these may contribute to iatrogenic fatigue and cognitive problems.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the College of Arts and Sciences have examined a thesis titled “Polypharmacy in Patients with Multiple Sclerosis: Effects on Fatigue, Perceived Cognition, and Objective Cognitive Performance,” presented by Joan M. C. Thelen, candidate for the Master of Arts degree, and certify that in their opinion it is worthy of acceptance.

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CHAPTER 1

OVERVIEW

Polypharmacy, or the use of multiple medications, is widespread among patients with multiple sclerosis (MS), who often have a variety of symptoms and comorbid health conditions. Polypharmacy is known to compound the risk of adverse drug effects, which may include impaired cognition and sedation (Haider, Johnell, Thorslund, & Fastbom, 2008). Although cognitive impairment and fatigue are common symptoms of MS, the relative contribution of polypharmacy to these symptoms is understudied. We examined the relationship between polypharmacy and measures of fatigue, perceived cognition, and objective cognition in a group of MS patients.

MS is the most common neurological disorder affecting young and middle-aged adults, typified by demyelination in the central nervous system (CNS) that leads to a broad spectrum of physical, cognitive, and emotional sequelae (Sadovnick & Ebers, 1993). Common symptoms of MS include numbness or tingling, pain, spasticity, sensory disturbances, depression, and sexual dysfunction (Crayton & Rossman, 2006; Goldstein, Siroky, Sax, & Krane, 1982; Poser, 1980). Fatigue is highly prevalent in MS, and many patients describe it as their most debilitating symptom (Krupp, Alvarez, LaRocca, & Scheinberg, 1988). In addition, cognitive impairment affects most individuals with MS at some point in their disease, typically in the domains of information processing speed, memory, and executive functioning (DeLuca, Johnson, & Natelson, 1993; Peyser, Edwards, Poser, & Filskov, 1980). Both cognitive dysfunction and fatigue are associated with negative

outcomes for employment, social relationships, and activities of everyday living (Benedict et al., 2005; Fisk, Ritvo, et al., 1994; Freal, Kraft, & Coryell, 1984; Rao et al., 1991).

In order to manage the wide array of symptoms caused by MS, patients frequently use additional medications together with their disease-modifying therapy. Many symptomatic drugs, such as benzodiazepines, opiate analgesics, and anticholinergics, are known to produce side effects, which can include sedation and cognitive impairment (Hindmarch, 2009; Klausner & Steers, 2007; Mula & Trimble, 2009). Patients may also use medications for conditions unrelated to their MS diagnosis, like hypertension or allergies. When patients use multiple medications on a daily basis, the risk of experiencing adverse drug effects increases exponentially (Astrand, Astrand, Antonov, & Petersson, 2007). Polypharmacy may therefore contribute to fatigue and cognitive impairment in MS patients.

Most polypharmacy studies have focused largely on elderly populations, as older adults are more likely to use a variety of medications to treat multiple ailments. Among the elderly, polypharmacy is associated with decreased functional ability, increased risk of falls, increased cognitive impairment, and increased mortality (Jyrkka, Enlund, Korhonen, Sulkava, & Hartikainen, 2009a, 2009b; Jyrkka, Enlund, Lavikainen, Sulkava, & Hartikainen, 2011; Moore & O'Keeffe, 1999; Onder et al., 2012). However, studies investigating polypharmacy effects in MS are limited.

The present study sought to examine the potential relationship between polypharmacy and measures of fatigue and cognition in MS. We used retrospective analysis of medication use among a group of patients who participated in a study investigating treatment adherence in individuals with MS (Bruce, Hancock, Arnett, & Lynch, 2010). The project achieved the following aims:

- 1) Examine the differential effects of polypharmacy on fatigue and cognition between MS patients and healthy controls. We hypothesized that patients with MS who take five or more medications would exhibit significantly more problems with fatigue and cognition than MS patients taking four or fewer medications and control participants.
- 2) Examine the impact of medications known to have detrimental effects on CNS functioning. We hypothesized that MS patients taking medications with detrimental CNS effects (e.g., opioids, benzodiazepines, etc.) would exhibit impairments in cognition and increased fatigue compared to MS patients who do not take medications with unfavorable CNS effects and controls.

Significance: Individuals with MS frequently experience fatigue and cognitive impairment, causing significant disruptions in employment, social relationships, and everyday living (Julian, 2011; Rao et al., 1991; Wu, Minden, Hoaglin, Hadden, & Frankel, 2007).

Understanding the relationship between polypharmacy and these symptoms can inform clinicians and researchers who make decisions for treatment plans and study designs involving patients with MS.

CHAPTER 2

REVIEW OF LITERATURE

Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic, autoimmune demyelinating condition of the central nervous system (CNS), typified by lesions (“scleroses”) in the brain and spinal cord. These lesions interrupt neural connections and cause individuals with MS to experience a broad variety of physical, cognitive, and emotional symptoms. MS affects approximately 1 in 1000 people in Europe and North America, while the prevalence is much lower in Asia and South America (Koch-Henriksen & Sorensen, 2010; Kurtzke, 1975). Disease onset typically occurs between ages 20 and 45, often striking young adults in their prime years (Sadovnick & Ebers, 1993), and disproportionately affecting women at a rate of 2:1 (Brassington & Marsh, 1998; Greer & McCombe, 2011). Although the exact cause of MS is unknown, it is currently believed to result from a combination of genetic predisposition and environmental factors. Family studies show that first-degree relatives of individuals with MS are at 15 to 35 times the risk of developing MS compared to the general population, whose risk is 0.1% (Sadovnick, Baird, & Ward, 1988). The concordance rate among monozygotic twins exceeds the rate found in dizygotic twins (25.4% and 5.4%, respectively) (Willer, Dyment, Risch, Sadovnick, & Ebers, 2003). Furthermore, maternal half-siblings have essentially the same risk as full siblings (2.35% and 3.11%, respectively, $p = .1$), while paternal half-siblings have a lower risk (1.31%), implicating a maternal genetic effect (Ebers et al., 2004).

Geographically, the prevalence of MS tends to be lower in regions near the equator, potentially implicating factors such as UV exposure or vitamin D deficiency (Disanto et al.,

2011; Ramagopalan et al., 2011; Simpson, Blizzard, Otahal, Van der Mei, & Taylor, 2011); However, in some regions of Europe the prevalence of MS varies greatly along the same latitude (Koutsouraki, Costa, & Baloyannis, 2010; Poser, 1994; Pugliatti, Sotgiu, Solinas, Castiglia, & Rosati, 2001). Evidence from migration studies suggest that MS susceptibility is more closely linked to geographical location in the first fifteen years of life, such that the risk of developing MS does not change for immigrants who relocate after adolescence (Elian, Nightingale, & Dean, 1990; Hogancamp, Rodriguez, & Weinshenker, 1997). Exposure to the Epstein-Barr virus (EBV) may also play a role in developing MS. Greater than 99% of MS patients have been infected with EBV, although the rate is 94% in the general population (Ascherio & Munger, 2007; Haahr, Plesner, Vestergaard, & Hollsberg, 2004). Individuals with a high plasma concentration of EBV-specific antibodies are at a higher risk of developing MS than those with a low concentration (Levin et al., 2005), and people with MS are more likely to have a past history of infectious mononucleosis, which is thought to reflect later-onset of EBV infection (Nielsen et al., 2007; Ramagopalan et al., 2009).

Symptomology and Subtypes. One hallmark of MS is the unpredictable and variable nature of its symptoms, which can suddenly appear and then disappear for months at a time. Symptoms of MS vary widely across individuals and can include physical, cognitive, and emotional disturbances. Some of the most frequently observed symptoms include numbness or loss of sensation, spasticity, ataxia, fatigue, mood changes, visual disturbances, cognitive impairment, loss of bowel or bladder control, and sexual dysfunction (Crayton & Rossman, 2006; Goldstein et al., 1982; Poser, 1980). The nature and severity of symptoms also depends on the MS disease subtype, such that progressive forms of the disease are associated with more advanced disability and greater symptom burden.

There are four different subtypes of MS based on the progression of the disease (Lublin & Reingold, 1996). Initially, most patients (~85%) are diagnosed with relapsing-remitting MS (RRMS), characterized by isolated relapses (often called “attacks,” “exacerbations,” or “flare-ups”) of symptoms, followed by recovery (Confavreux & Vukusic, 2006). A majority of these RRMS patients will slowly experience a progressive decline in function after approximately ten years of disease onset. This subtype is called secondary progressive MS (SPMS). About 15% of patients experience a general progressive decline beginning at the very onset of disease, labeled primary progressive MS (PPMS) (Miller & Leary, 2007). In a small number of cases, this progressive development of disability is experienced in addition to relapses, called progressive relapsing MS (PRMS) (Tullman, Oshinsky, Lublin, & Cutter, 2004).

Diagnosis. There is no single test that can be performed to diagnose MS. Rather; the physician must accumulate evidence indicative of MS while excluding alternative explanations for the symptoms (Polman et al., 2011). The main criterion in diagnosing MS is the demonstration of lesions in the CNS that are disseminated in time and space (Poser & Brinar, 2001). Dissemination in time requires that symptomatic episodes must be separated by at least 30 days to constitute distinct neurological events or the presence of active gadolinium enhancing lesions and older non-enhancing lesions. Dissemination in space necessitates symptoms or lesions that involve at least two distinct areas of the CNS (i.e., juxtacortical, infratentorial, periventricular, and/or spinal cord) (McDonald et al., 2001). The most sensitive and specific method of obtaining objective evidence of lesions is magnetic resonance imaging (MRI). In some cases, analysis of cerebrospinal fluid (CSF) and visual evoked potentials (VEP) are used to obtain supportive evidence (McDonald et al., 2001).

Objective clinical evidence can be obtained via neurological examination. Symptoms indicative of MS, either reported by patients or observed objectively, must last at least 24 hours in the absence of fever or infection to constitute an attack (McDonald et al., 2001). The most recent revision to the McDonald diagnostic criteria was published in 2010 and can be used by physicians to simplify and hasten the process of determining an MS diagnosis (Polman et al., 2011).

Treatment. There is currently no cure for MS. Recovery from acute symptom relapses can be accelerated by steroid treatment, most commonly involving a high dose of intravenous methylprednisolone over the course of several days (Milligan, Newcombe, & Compston, 1987; Patzold, Schwengelbeck, Ossege, Malin, & Sindern, 2002). Additionally, MS patients are usually prescribed a disease-modifying therapy (DMT), which prevents future relapses and wards off further development of disability. The most frequently prescribed DMTs are interferon beta (IFN β), glatiramer acetate (GA), natalizumab, and mitoxantrone, although several others exist (Buck & Hemmer, 2011). These medications have been shown to moderate MRI-associated disease activity and reduce relapse rates (Samkoff & Goodman, 2011), but can produce significant side effects and are often expensive (Minen & Karceski, 2011). Furthermore, IFN β , GA, and natalizumab are administered either via intramuscular or subcutaneous injection, which is often burdensome to the patient and can cause adverse reactions at the injection site. Although DMTs can reduce the likelihood of future CNS damage, they do not restore neurologic function and have no observable, immediate benefit to patients. For these reasons, long-term adherence to DMTs is often poor among individuals with MS (Beer et al., 2011; O'Rourke & Hutchinson, 2005; Rio et al., 2005).

Other medications specifically target the various symptoms that individuals may experience as a result of MS, such as spasticity, fatigue, bladder difficulties, or pain (Frohman et al., 2011). Such treatments can vary in category and quantity depending on the presence and severity of symptoms exhibited by an individual.

Spasticity. Muscle spasms, along with difficulty initiating and controlling muscle movement, are experienced in approximately 75% of patients with MS (Rizzo, Hadjimichael, Preiningerova, & Vollmer, 2004). Baclofen acts on gamma-aminobutyric acid (GABA) receptors to reduce motor neuron activity (Shakespeare, Boggild, & Young, 2003), and has been shown to be effective in treating spasticity in MS (Kheder & Nair, 2012; Smith, LaRocca, Giesser, & Scheinberg, 1991). Side effects of baclofen include daytime sedation and muscle weakness (Sawa & Paty, 1979). Tizanidine can also be used to treat spasticity by reducing muscle tone, but side effects can include sedation and dizziness (Nance et al., 1997). Diazepam and gabapentin are both GABAergic drugs that may be used for spasticity, but their usefulness may be moderated by their sedative effects (Samkoff & Goodman, 2011).

Pain. Up to 86% of MS patients report pain as a troubling symptom (Bermejo, Oreja-Guevara, & Diez-Tejedor, 2010; O'Connor, Schwid, Herrmann, Markman, & Dworkin, 2008). The pain experienced by individuals with MS may have various origins. Lesions in the CNS can cause neuropathic pain, which can be alleviated with antiepileptic agents (including lamotrigine, gabapentin, and topiramate), tricyclic antidepressants (such as amitriptyline) and serotonin-norepinephrine reuptake inhibitors (venlafaxine and duloxetine) (Ben-Zacharia, 2011; Boissy & Cohen, 2007; Pollmann & Feneberg, 2008). Again, many of these drugs can cause adverse side effects, including sedation and cognitive impairment

(Mula & Trimble, 2009; Peretti, Judge, & Hindmarch, 2000). Alternatively, MS may indirectly elicit pain that results from musculoskeletal disturbances and spasticity. This type of pain is usually treated in the same way as in neurologically-intact populations, such as with non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen or naproxen (Eccles, Freemantle, & Mason, 1998).

Bladder dysfunction. Urinary tract and neurogenic bladder dysfunction may affect up to 70% of individuals with MS (Fowler et al., 2009), and 90% of patients who have had the disease for ten or more years (Andersson & Pehrson, 2003). Bladder symptoms, often caused by spinal lesions, may manifest as increased urinary urgency and frequency, urinary retention and incontinence, or overflow incontinence and incomplete emptying (Del Popolo, Panariello, Del Corso, De Scisciolo, & Lombardi, 2008). Bladder symptoms in MS are typically treated with anticholinergic medications, including oxybutynin, tolterodine, and darifenacin (Henze, Rieckmann, & Toyka, 2006; Samkoff & Goodman, 2011). Adverse side effects of anticholinergic drugs can include cognitive dysfunction, fatigue, and dizziness (Klausner & Steers, 2007).

Depression. People with MS experience depression at a higher rate than the general population, with a lifetime prevalence of around 50% and point prevalence ranging from 15 to 50% (Chwastiak et al., 2002; McGuigan & Hutchinson, 2006; Siegert & Abernethy, 2005). Depression in MS can be treated effectively with psychotherapy and/or antidepressant medication (Mohr, Boudewyn, Goodkin, Bostrom, & Epstein, 2001; Walker & Gonzalez, 2007). Pharmaceutical treatments for depression may include selective serotonin reuptake inhibitors (SSRIs), serotonin antagonist and reuptake inhibitors (SARIs), tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, or other atypical antidepressants

(including bupropion, duloxetine, and venlafaxine) (Barak, Ur, & Achiron, 1999; Ehde et al., 2008; Koch, Glazenborg, Uyttenboogaart, Mostert, & De Keyser, 2011). Some of these drugs, in particular the older tricyclic antidepressants and MAO inhibitors, are often accompanied by sedating side effects and cognitive dysfunction (Cassano & Fava, 2004; Kyle, Petersen, & Overo, 1998).

Polypharmacy

Polypharmacy, or the use of multiple medications, increases the risk of adverse drug reactions (ADRs). Virtually all drugs have the potential for adverse side effects. For each additional medication that is prescribed, the likelihood of interaction effects increases exponentially. Wright and colleagues (2012) outlined the ADRs that may arise as a result of using multiple concurrent medications, either through pharmacokinetic or pharmacodynamic actions: (1) a drug-drug interaction occurs when a medication's activity or therapeutic effect is altered by another medication; (2) therapeutic duplication occurs when a patient uses two medications from the same drug class that have overlapping therapeutic effects; (3) drug duplication occurs when different formulations of the same drug are given, or combination products containing the same drug are used (e.g., hydrocodone-acetaminophen and acetaminophen-chlorpheniramine-phenylephrine); and (4) additive effects occur when two drugs are not of the same class and do not interact, but still have overlapping therapeutic effects (Wright et al., 2012).

Therefore, the possible effects of polypharmacy (five to nine medications) and excessive polypharmacy (ten or more medications) (Haider et al., 2008) are highly unpredictable and potentially dangerous. In fact, one study reported that the number of drugs

per patient was the sole independent predictor of ADR-related hospital admissions, and 18.6% of these ADRs were coded as severe (Alexopoulou et al., 2008).

Beyond the specific pharmacokinetics and pharmacodynamics of a given drug, it is also crucial to consider individual characteristics of the patient that may influence clinical drug effects and potential interactions. Such variables include gender, co-morbid conditions, lifestyle factors (such as diet, alcohol, or tobacco use), and age (Prybys, 2004).

Polypharmacy in Older Adults. Due to the physiological and metabolic changes that occur as part of the normal aging process, older adults are typically more susceptible to adverse medication effects. It is typical for older adults to develop chronic, age-related conditions, such as arthritis, hypertension, and heart disease, leading the elderly to consume a disproportionate quantity of prescription and OTC drugs (Gu, Dillon, & Burt, 2010). For this reason, polypharmacy has been studied most extensively in older populations with chronic conditions (Moore & O'Keeffe, 1999; Onder et al., 2012; Salazar, Poon, & Nair, 2007). In a study of women with chronic kidney disease (CKD), it was determined that women 50 years and older were over four times more likely to be prescribed five or more medications compared to younger women aged 18 to 34 (Rasu, Jayawant, Abercrombie, & Balkrishnan, 2009). In community-dwelling elderly adults, excessive polypharmacy has been associated with poor outcomes, including decreased functional ability in activities of daily living, impaired cognitive functioning, poorer nutritional status, increased falls, and increased mortality (Corsinovi et al., 2009; Heuberger & Caudell, 2011; Jyrkka et al., 2009a, 2009b; Jyrkka et al., 2011; Larson, Kukull, Buchner, & Reifler, 1987; Richardson, Ananou, Lafortune, Brayne, & Matthews, 2011).

Polypharmacy in MS. Currently, the effects of polypharmacy in individuals with multiple sclerosis are unknown. It is common for individuals with MS to use a variety of medications, which may include disease-modifying therapies, symptomatic drugs, and medications for other conditions unrelated to MS. Some researchers have specifically explored medications with potential cognitive side effects, including drugs that are active within the CNS. Oken and colleagues (2006) examined the cognitive and fatigue effects of medications in a sample of 70 MS patients. They divided the sample into two groups: patients that used at least one CNS-active medication, and patients that used no medications with CNS effects. After comparing the two groups, analysis revealed that patients using CNS-active drugs reported more fatigue and performed worse on measures of attention and processing speed; however, these effects disappeared after controlling for physical disability and depression, which may in fact be the reason they were using CNS-active drugs in the first place.

Drug activity in the CNS. A variety of drug classes are known to have deleterious CNS side effects, including anticholinergics, benzodiazepines, sedative-hypnotics, and anticonvulsants, among others. Many of these medications have been associated with functional impairments in studies examining polypharmacy in older adults (Kallin, Gustafson, Sandman, & Karlsson, 2004; Klausner & Steers, 2007; Peron, Gray, & Hanlon, 2011; Shoair, Nyandege, & Slattum, 2011; Sittironnarit et al., 2011). For example, anticholinergics are widely known to produce a number of central side effects, which can include blurred vision, increased heart rate, sedation, confusion, agitation, and inability to concentrate (Tune, 2001). Furthermore, the anticholinergic effect of slowed gastrointestinal motility may cause other drugs to spend more time in the small intestine, leading to a longer

duration of direct contact with the mucosal lining and higher rates of drug absorption (Prybys, 2004). In his review of cognitive side effects of medications, Meador (1998) reported that slowed psychomotor speed and impaired vigilance are the most common cognitive impairments associated with centrally-acting drugs. Compared to other aspects of cognition, it is believed that the brain's alertness and attentional systems are disproportionately affected by drugs, particularly those that directly involve neurotransmitters in the nonspecific cortical projection system (i.e., serotonin, norepinephrine, dopamine, acetylcholine, and histamine) or the more broadly distributed cortical neurotransmitters, such as GABA (Oken et al., 2006). For this reason, polypharmacy that involves centrally-acting drugs increases the risk of cognitive impairment and other unfavorable effects (Meador, 1998).

Fatigue in MS

A standard definition of MS-related fatigue is “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities,” according to the MS Council for Clinical Practice Guidelines (1998). Fatigue is experienced by up to 92% of individuals with MS over the course of their disease (Branas, Jordan, Fry-Smith, Burls, & Hyde, 2000). As many as 40% of patients with MS report fatigue as their most debilitating symptom (Krupp et al., 1988), as it interferes profoundly with employment, family obligations, social relationships, and overall quality of life (Freal et al., 1984; Schwartz, Coulthard-Morris, & Zeng, 1996). Fatigue is also associated with poorer perceived health, as reported by patients (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994). The negative consequences of fatigue in MS can be so

significant that the US Social Security Administration cites it as a criterion for granting disability (Federal Old-Age, 1950-).

The cause of fatigue in MS is complex and suspected to result from a variety of pathways (Lapierre, 2007; MacAllister & Krupp, 2005). One possible mechanism of fatigue in MS is immune system dysregulation, potentially due to increased levels of pro-inflammatory cytokines associated with MS lesion activity (Heesen et al., 2006; Leocani, Colombo, & Comi, 2008; Schwid, Covington, Segal, & Goodman, 2002). Fatigue may also result from alterations in specific regions of the CNS, such as the primary sensorimotor area (Riccitelli et al., 2011), hypothalamus (Davis, Wilson, White, & Frohman, 2010), or basal ganglia (DeLuca, Genova, Hillary, & Wylie, 2008). These brain regions are partly responsible for sustaining neural activity, arousal, and thermoregulation, and demyelination or axonal loss in these areas may disrupt these processes. Similarly, it has been suggested that neuroendocrine abnormalities in MS patients are related to overactivation of the hypothalamo-pituitary-adrenal (HPA) axis (Huitinga, Erkut, van Beurden, & Swaab, 2003), and may result in fatigue (Gottschalk et al., 2005). Although fatigue in MS is often attributable to pathological dysfunction within the CNS, other ancillary factors can be a significant source of fatigue for patients.

Primary and Secondary Fatigue. It is necessary to differentiate primary fatigue, caused directly by MS disease activity, from secondary fatigue, which stems from conditions related to MS diagnosis, including depression, infections, sleep problems due to pain and spasms, or metabolic disorders such as hypothyroidism (Kos, Kerckhofs, Nagels, D'Hooghe M, & Ilsbroukx, 2008). Another common source of secondary fatigue in MS may be medication side effects. Individuals with MS use various categories of medications to treat or

relieve their symptoms, and many of these pharmaceutical agents can cause fatigue as a side effect, including antispasticity agents, narcotic analgesics, anticonvulsants, immunomodulators, muscle relaxants, and sedative-hypnotics (Ben-Zacharia, 2011; Frohman et al., 2011; Lapierre, 2007). Furthermore, it is relatively common for individuals with MS to combine two or more of these drugs to control multiple symptoms, and the fatiguing effects of such drug interactions are not adequately understood.

Treatment of Fatigue. Many patients with MS are prescribed medications to reduce fatigue or increase attention and alertness, such as amantadine, pemoline, fampridine, and modafinil (Penner & Calabrese, 2010). Amantadine has been shown to produce moderate improvements in fatigue in placebo-controlled trials (Cohen & Fisher, 1989; Krupp et al., 1995). However, a systematic review by Brañas and colleagues identifies some methodological flaws that may undermine these findings, such as period or carryover effects from crossover trials and lack of clinically significant fatigue outcome measures (Branas et al., 2000). Evidence for the effectiveness of pemoline is mixed (Krupp et al., 1995; Weinshenker, Penman, Bass, Ebers, & Rice, 1992). Furthermore, pemoline may be inappropriate for treating chronic fatigue in MS due to its potential for liver toxicity (Berkovitch, Pope, Phillips, & Koren, 1995). In one randomized, double-blind, placebo controlled trial, fampridine yielded improvements in lower muscle extremity strength and walking speed, but no significant changes in fatigue rating scores. Furthermore, side effects included tingling, dizziness, and at high doses, convulsions (Goodman et al., 2007). Early trials of modafinil supported the drug's efficacy in terms of promoting wakefulness and reducing fatigue in patients with MS (Brioschi et al., 2009; Rammohan et al., 2002);

however, a more recent and methodologically rigorous study contradicts these claims (Moller et al., 2011).

Overall, these findings indicate that no “gold standard” exists for treating MS-related fatigue, and further studies are warranted to determine the effectiveness of current treatments. Accordingly, clinicians and researchers need to explore alternative methods for alleviating fatigue among MS patients. One such method may involve reducing the overall number of daily medications, thereby minimizing potential side effects and drug interactions. If fatigue is experienced as an iatrogenic effect of polypharmacy, it is possible that eliminating or reducing polypharmacy would decrease fatigue and improve MS patients’ overall quality of life.

Cognitive Impairment in MS

Between 40 - 70% of patients with MS experience cognitive impairment (Beatty, 1993; Bobholz & Rao, 2003; Rao et al., 1991), which can occur at any stage in the disease (Amato, Zipoli, & Portaccio, 2006; Feillet et al., 2007; Schulz, Kopp, Kunkel, & Faiss, 2006; Zipoli et al., 2010). It is typical for cognitive problems to persist once they arise, and often worsen over time (Amato, Ponziani, Siracusa, & Sorbi, 2001; Kujala, Portin, & Ruutiainen, 1997). Although patients with progressive forms of MS tend to develop more severe cognitive impairment than those with a relapsing-remitting course (Huijbregts et al., 2004), deficits are only modestly associated with overall disability level (Lynch, Parmenter, & Denney, 2005). Patients with cognitive dysfunction often experience difficulties related to employment, personal relationships, medication adherence, and everyday functional activities (Benedict et al., 2005; Bruce, Hancock, et al., 2010; Kalmar, Gaudino, Moore, Halper, & Deluca, 2008; Rao et al., 1991).

Common Types of Cognitive Impairment. Although many cognitive functions can be affected in MS, the most common impairments are seen in information processing speed, working memory, executive function, and long-term memory (DeLuca et al., 1993; Denney, Lynch, Parmenter, & Horne, 2004). Deficits in these areas may subsequently influence other cognitive functions, such as visuospatial abilities and language (Jonsson et al., 2006; Mackenzie & Green, 2009).

Speeded Information Processing. Reduced information processing speed is described as one of the primary cognitive deficits in MS, and exists in up to 50% of patients (Benedict, Cookfair, et al., 2006; DeLuca, Chelune, Tulskey, Lengenfelder, & Chiaravalloti, 2004; Rao et al., 1991). Problems in this area may manifest as slowed response times (Achiron et al., 2007) along with concurrent decrements in memory, attention, and executive function (Chiaravalloti & DeLuca, 2008; Drew, Starkey, & Isler, 2009; Lengenfelder et al., 2006). Among MS patients, slowed processing speed has been associated with depressed mood, fatigue, and memory impairments (Archibald & Fisk, 2000; DeLuca et al., 2004; Diamond, Johnson, Kaufman, & Graves, 2008), and may significantly contribute to health-related quality of life (Barker-Collo, 2006).

Executive Function. Up to a quarter of MS patients demonstrate impairments in executive functioning, which encompasses a broad set of behaviors including planning, organization, task-setting, and abstract reasoning (Henry & Beatty, 2006; Rao et al., 1991; Schulz et al., 2006). Patients' subjective ratings of executive dysfunction are suggested to predict overall neuropsychological impairment and poorer functional outcomes (Basso et al., 2008). Furthermore, impaired executive functions may lead to negative outcomes among patients with MS, such as poor adherence to complex treatment regimens, reduced coping

abilities, and difficulty making decisions about medical treatment (Basso et al., 2010; Goretti, Portaccio, Zipoli, Razzolini, & Amato, 2010; Possa, 2010).

Memory. Memory is conceptualized as the ability to store, preserve, and recall information and experiences. Between 40 – 65% of people with MS experience memory impairments (Chiaravalloti & DeLuca, 2008), which can interfere with work, social relationships, and activities of everyday living. Initially, it was believed that memory deficits in MS were due to obstacles in retrieval from long-term storage (Rao, Leo, & St Aubin-Faubert, 1989), but later studies suggest that memory problems are caused by deficits in the initial learning of information, as MS patients require more exposures to encode stimuli than healthy controls (DeLuca, Barbieri-Berger, & Johnson, 1994). Memory problems in MS can be as variable as the disease itself. MS patients are not uniformly affected, even among those who do report difficulties with memory. Some authors suggest that immediate recall and delayed recall are both affected in MS, while incidental and remote memory remain relatively intact (Arnett & Strober, 2011). Others have found significant impairments in episodic memory (Brissart, Morele, Baumann, & Debouverie, 2012; Fuso, Callegaro, Pompeia, & Bueno, 2010), as well as verbal and spatial memory (Andrade et al., 1999; Jonsson et al., 2006; Scherer et al., 2007). Prospective memory, or the memory of future intentions, can also be affected in MS (Kardiasmenos, Clawson, Wilken, & Wallin, 2008; Rendell, Jensen, & Henry, 2007), and has major implications for medication adherence (Bruce, Hancock, et al., 2010).

Cause of Cognitive Impairment. The primary cause of cognitive impairment in MS is diffuse brain atrophy and grey matter atrophy (Amato et al., 2004; Benedict, Ramasamy, Munschauer, Weinstock-Guttman, & Zivadinov, 2009; Christodoulou et al., 2003; Morgen et

al., 2006). Recent investigations suggest that third ventricular width is the most predictive magnetic resonance imaging metric of cognitive impairment in MS, perhaps reflecting atrophy of the thalamus, an area responsible for communicating sensory information to the cerebral cortex (Benedict, Bruce, et al., 2006; Benedict et al., 2004). Other investigations have focused on secondary causes of cognitive dysfunction in MS, including depression, fatigue, personality changes, and medication side effects (Andreasen, Spliid, Andersen, & Jakobsen, 2010; Arnett, Barwick, & Beeney, 2008; Arnett, Higginson, & Randolph, 2001; Benedict, Priore, Miller, Munschauer, & Jacobs, 2001; Brunner et al., 2006; Oken et al., 2006). Secondary sources of cognitive impairment may not only affect objective performance, but also the individual's perception of their cognitive functioning.

Perceived Cognitive Difficulties

Objective cognitive impairment, as determined by deficits in cognitive performance on standardized neuropsychological tests, does not necessarily correlate with subjective impairment, based on patients' self-report (Basso et al., 2008; Kinsinger, Lattie, & Mohr, 2010; Middleton, Denney, Lynch, & Parmenter, 2006). In other words, patients may feel that their cognition is normal, when in fact they have significant impairments on objective tests of cognition. Similarly, sometimes patients feel like they are experiencing cognitive problems when, in reality, they are cognitively intact. Sometimes, this misperception is related to the presence of mood disorders. Depression, for example, may increase the perception of cognitive problems, leading patients to overestimate their impairments (Bruce & Arnett, 2004; Bruce, Bruce, Hancock, & Lynch, 2010; Maor, Olmer, & Mozes, 2001), and evidence suggests that successful treatment of depression improves the accuracy of subjective ratings of cognition (Julian, Merluzzi, & Mohr, 2007; Kinsinger et al., 2010).

Similarly, patients with MS often report that fatigue interferes with their cognitive functioning, such that their cognitive performance worsens during periods of heightened fatigue. However, in a study by Parmenter, Denney, and Lynch (2003), MS patients were tested across periods of low and high fatigue. Performance improved from the first testing session to the second, regardless of fatigue level, even though participants felt that their performance deteriorated during the high fatigue condition. This provides additional evidence that perceived deficits may be more highly related to fatigue than to actual performance.

Many of the medications used by patients with MS have side effect profiles that include reports of worse perceived cognition. By recognizing the relationship between polypharmacy and perceived cognition in patients with MS, clinicians and researchers can develop appropriate treatment plans and research techniques that account for this phenomenon.

Summary

Individuals with MS are frequently prescribed multiple medications to treat a wide range of physical, cognitive, and emotional symptoms. Fatigue and cognitive impairment are among the most common and troubling symptoms, as reported by patients. Many medications prescribed to treat MS symptoms can have adverse side effects, which may include lethargy and impaired cognition. Among older adults, polypharmacy is associated with poor outcomes, including CNS side effects and functional impairment. However, effects of multiple medications have not been widely explored in MS patients, thus the relationship between fatigue, cognitive impairment, and polypharmacy is currently unknown in this population.

The primary implications of this study are twofold. From a clinical standpoint, understanding the relationship between polypharmacy, fatigue, and cognition could help clinicians appraise treatment plans and make modifications that could lead to ameliorated symptoms. From a research perspective, if a strong association exists between polypharmacy and adverse drug effects, there should be a greater effort to control for these factors when executing studies that investigate the correlates of cognition and fatigue.

Goals and Hypotheses

The aims of this study were to investigate the effects of polypharmacy on perceived cognitive impairment, objective cognitive performance, and fatigue in patients with MS.

- 1) Examine the differential effects of polypharmacy on fatigue and cognition between MS patients and healthy controls. It is hypothesized that, after controlling for disease-related variables, participants with MS who take five or more medications have significantly more problems with fatigue and cognition than MS patients and controls taking four or fewer medications.
- 2) Examine the impact of medications known to have detrimental effects on CNS functioning. We hypothesize that MS patients taking medications with detrimental CNS effects (e.g., opioids, benzodiazepines, etc.) have impairments in cognition and increased fatigue compared to MS patients and controls who do not take medications with unfavorable CNS effects.

CHAPTER 3

METHOD

Participants

Eighty-six participants with MS were recruited through a large specialty clinic affiliated with the University of Kansas Medical Center. Participants were paid \$125 as compensation for their participation in a larger study examining treatment adherence in MS (Bruce, Hancock, et al., 2010). Criteria for inclusion included: (1) no nervous system disorder other than MS; (2) no severe sensory, motor, physical, or neurological impairment that would make participation in the study insurmountable; (3) no history of learning disability; (4) no current alcohol or drug abuse; (5) no relapse and/or corticosteroid treatment within four weeks of evaluation; and (6) current use of a self-injected disease modifying therapy for at least sixty days. Each subject had received an MS diagnosis based on established criteria (Polman et al., 2005) from a board-certified neurologist, who also rated patients based on Kurtzke's Expanded Disability Status Scale (Kurtzke, 1983). Twenty age- and education-matched controls were recruited using flyers posted throughout the community. Controls were paid \$50 for their participation in the study.

Procedure

This investigation is based on a secondary data analysis from a study examining treatment adherence in a sample of patients with MS (Bruce, Hancock, et al., 2010). Patients completed a psychiatric interview, questionnaires, and a battery of neuropsychological tests following acceptance into the study. All procedures were approved by the institutional review boards of the University of Missouri – Kansas City and the University of Kansas Medical Center.

Measures

Polypharmacy. Participants were asked to provide a complete list of all medications used on a daily basis, which was tallied to provide an estimate of polypharmacy. Those participants taking five or more daily medications were considered to be “with polypharmacy,” while patients taking four or less medications were considered to be “without polypharmacy.” The cutoff value of five medications to categorize polypharmacy status is frequently used in the literature (Fulton & Allen, 2005; Gnjidic et al., 2012; Haider et al., 2008; Jorgensen, Johansson, Kennerfalk, Wallander, & Svardsudd, 2001; Linjakumpu et al., 2002; Onder et al., 2012; Richardson et al., 2011) Medications that were prescribed for *pro re nata* (PRN) use (“as needed”) were not included in analyses. If a participant reported taking a PRN medication within 24 hours prior to the testing session, this was documented and considered in analyses accordingly. Furthermore, all medications were separated into two groups: those that are reported in the literature to have detrimental CNS effects, and those that have little or no CNS activity. This list was reviewed and confirmed by a board-certified neurologist (see Table A1 in Appendix). The specific mechanism of action for each potentially detrimental CNS drug and the corresponding adverse CNS effects are listed in Table A2 in the Appendix.

Emotional functioning. Depression was assessed with the Beck Depression Inventory – Fast Screen (BDI-FS) (Beck, 2000). The BDI-FS is a self-report questionnaire for depressive symptoms, and has been validated for use among MS patients (Benedict, Fishman, McClellan, Bakshi, & Weinstock-Guttman, 2003). Participants are asked to select a response to seven different items to indicate their mood in the previous two weeks. For example, the responses to item one range from “I do not feel sad” (0 points) to “I am so sad

or unhappy that I can't stand it" (3 points). Higher scores are indicative of more depressive symptoms.

Participants' self-reported fatigue was measured with the Modified Fatigue Impact Scale (MFIS) (Fisk, Ritvo, et al., 1994). The MFIS is frequently used in MS research to assess the impact of fatigue. A five-item version for the MFIS was used in this sample. This abbreviated version is highly correlated with the longer, 21-item version of the measure (Ritvo, 1997). Participants were asked to rate how much their fatigue had affected them during the past four weeks, using a five-point scale. Higher scores are indicative of more fatigue.

Cognitive functioning. Processing speed was measured with the Symbol Digit Modalities Test (SDMT) (Smith, 1982). The SDMT assesses information processing speed by requiring patients to quickly say a number that matches a corresponding symbol. The dependent variable is the number of correct responses in 90 seconds. The oral form of the SDMT was used in this sample.

Attention was measured with the Stroop Color-Word Trial (Stroop, 1935). The Stroop task is a common test of inhibition and selective attention, and is considered to be sensitive to frontal lobe function (Pardo, Pardo, Janer, & Raichle, 1990). Participants are asked to respond to words on a computer screen by stating the color of the text, rather than reading the actual word aloud. The dependent variable is the number of correct responses in 45 seconds.

Verbal memory was assessed with the Auditory Verbal Learning Test (AVLT) (Lezak, 1995). Over several trials, participants are required to learn and then immediately recall a list of 15 unrelated words. The final trial occurs following a 20-minute delay. An

abbreviated version of the instrument was used in this study, which comprised three learning trials and a delayed recall trial.

Prospective memory, or the ability to remember to carry out a future task, was measured with the Memory for Intentions Screening Test (MIST) (Woods, Moran, Dawson, Carey, & Grant, 2008). This standardized test of ‘memory for future intentions’ requires participants to generate verbal and motor reactions in response to a visual cue or after a specified time delay. Tasks are designed to mimic everyday tasks that would occur in real life. For example, in one time-based task, the examiner says to the participant, “In 15 minutes, tell me that it is time to take a break.” A shortened version of the test was used, consisting of two event-based tasks and two time-based tasks.

Perceived cognitive functioning. Self-reported memory problems were assessed with the Prospective and Retrospective Memory Questionnaire (PRMQ) (Smith, Della Sala, Logie, & Maylor, 2000). The PRMQ is a 16-item self-report measure of prospective and retrospective memory failures in everyday life. Half of the items assess prospective memory (e.g., “Do you forget appointments if you are not prompted by another person or reminders such as a calendar?”) and the other half assesses retrospective memory (e.g., “Do often forget details from recent conversations?”). Participants rank their response to items on a five-point scale, ranging from 1 (*never*) to 5 (*very often*).

Self-reported problems with speeded processing was measured with the Processing Speed Difficulties Scale (PSDS) (Roberg, Bruce, Lovelace, & Lynch, 2012). The PSDS is a ten-item self-report tool that measures participants’ subjective experiences of slowed cognitive processing. Examples of items include, “It is difficult for me to think quickly” and

“It is hard for me to follow rapid speech.” Item responses are ranked on a seven-point scale, ranging from 1 (*never*) to 7 (*all the time*).

Self-reported frequency of dissociative experiences was assessed using the Dissociative Experiences Scale-II (DES) (Bernstein & Putnam, 1986; Carlson & Putnam, 1993). The DES is a 28-item self-report measure of dissociative experiences, which may range from mild detachment to one’s immediate surroundings (such as daydreaming or “zoning out”) to more acute detachment from one’s emotional or physical experiences. Participants are asked to estimate the percentage of time that they experience various dissociative incidents, such as absorption, depersonalization, segment amnesia, and in situ amnesia. Past research suggests that dissociative experiences are associated with perceived executive deficits, but not objective neuropsychological impairment (Bruce, Ray, Bruce, Arnett, & Carlson, 2007). Additionally, certain types of medications have been associated with disorienting side effects (Green, Roback, Kennedy, & Krauss, 2011; Jackson, Doherty, & Coulter, 2008), which may induce or mimic dissociative experiences.

Physical functioning. Level of disability was assessed with the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The EDSS is a measure of MS disease progression and neurological impairment. It 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.

Statistical Analyses

The first aim was to examine differences between MS patients with ≥ 5 medications, MS patients with < 5 medications, and healthy controls on the self-report measures. This was assessed using multivariate analysis of covariance (MANCOVA). In cases where the

assumption of homogeneity was violated, a nonparametric version of MANCOVA was performed, using ranked variables in place of the raw data. As described by Finch (2005) and consistent with our prior work (Bruce, Harrington, Foster, & Westervelt, 2009), a chi-square statistic can be calculated based on Pillai's trace, such that $\chi^2 = (n - 1) V$, where n = sample size and V = Pillai's trace. The initial analysis compared all three groups, controlling for age. Follow-up ANCOVAs were then performed to determine the nature of group differences on each of the measures that were significant in the overall comparison. Both of the MS groups were compared against the controls in separate analyses, again using age as a covariate. Finally, the two MS groups were compared to each other using age, duration of MS diagnosis, and disability (EDSS) as covariates. This procedure was then repeated to assess differences in the objective cognitive measures.

The second aim of the study was to assess the degree to which drugs with unfavorable CNS effects alter cognition and fatigue in MS patients. Participants with MS were separated into two groups: those taking one or more medications with unfavorable CNS effects and those taking no CNS-detrimental medications. To examine differences on the self-report measures, both groups of MS patients were compared to controls in a MANCOVA, with age as a covariate. As described above, a nonparametric version of MANCOVA was used when the assumption of homogeneity was violated. Follow-up ANCOVAs were then performed on the variables that were significant in the overall MANCOVA to determine the nature of group differences. To assess differences in the objective cognitive measures, the procedure was repeated using MANCOVA and follow-up ANCOVAs.

An additional exploratory analysis was performed to examine the bivariate relationships between the number of medications and fatigue, perceived cognition, and

objective cognition. This was assessed using Spearman's r correlation coefficients, with $p < .05$ indicating significant correlations. These analyses were followed by partial Spearman correlations to control for the effects of age, duration of diagnosis, and overall disability.

CHAPTER 4

RESULTS

Descriptive Data

The sample included 86 patients with MS, 75 of whom were women (87.2%). The average age was 47.17 ± 10.56 years, and patients had an average of 14.90 ± 1.93 years of education. Eighty-seven percent (n=75) were diagnosed with relapsing remitting MS, 10.5% (n=9) with secondary progressive MS, and 2.3% (n=2) with primary progressive MS. The patients were primarily Caucasian (88.4%, n=76), followed by African American (5.8%, n=5), Hispanic/Latino (3.5%, n=3), and 'other' (1.2%, n=1). The average duration of diagnosis was 10.38 ± 8.37 years, and the average EDSS score was 2.74 ± 1.53 . On average, participants took 3.72 ± 2.75 prescription medications per day (range: 1-17). Polypharmacy status was determined using the criteria of at least five daily medications, a value commonly reported in the polypharmacy literature (Onder et al., 2012; Rasu et al., 2009; Salazar et al., 2007). Patients taking four or fewer daily medications were considered to be without polypharmacy. In this sample of MS patients, 32.9% (n=28) met criteria for polypharmacy. Furthermore, 62.4% (n=53) were using at least one medication with potentially unfavorable CNS effects. Medications were categorized by CNS effects, as shown in Appendix A.

Among the participants with MS, the following comorbid conditions were reported: hypertension (n=14), asthma (n=4), hypercholesterolemia (n=4), depression (n=3), diabetes (n=2), fibromyalgia (n=2), hypothyroidism (n=2), arthritis (n=2), sleep apnea (n=1), narcolepsy (n=1), glaucoma (n=1), basal motor rhinitis (n=1), bipolar disorder (n=1), irritable bowel syndrome (n=1), macular degeneration (n=1), gastroesophageal reflux disease (n=1), spinal stenosis (n=1), esophageal stenosis (n=1), osteopenia (n=1), scoliosis (n=1),

hemochromatosis (n=1), rosacea (n=1), psoriasis (n=1), history of melanoma (n=1), benign hypermobility joint syndrome (n=1), in situ carcinoma (n=1), and history of obsessive-compulsive disorder (n=1).

Twenty healthy controls were also included in the study, matched for age and education with the MS patients. Eighty-five percent (n=17) were women, with an average age of 45.4 ± 10.9 years, and an average education of 15.75 ± 1.94 years. Ninety percent of the controls were Caucasian (n=18) and ten percent (n=2) were African American. No comorbid health conditions were reported for the controls. The average number of daily medications was 0.85 ± 1.04 (range: 0-4). See Table 1.

Table 1

Descriptive Characteristics of the Sample

	MS Patients <i>n</i> (%) or Mean (<i>SD</i>)	Controls <i>n</i> (%) or Mean (<i>SD</i>)
Gender		
Female	75 (87.2%)	17 (85%)
Male	11 (12.8%)	3 (15%)
Race		
Caucasian	76 (88.4%)	18 (90%)
African American	5 (5.8%)	2 (10%)
Hispanic/Latino	3 (3.5%)	...
Other	1 (1.2%)	...
Age (years)	47.17 (10.56)	45.40 (10.90)
Education (years)	14.90 (1.93)	15.75 (1.94)
Number of daily medications	3.72 (2.75)	0.85 (1.04)
MS subtype		
Relapsing Remitting	75 (87.2%)	...
Secondary Progressive	9 (10.5%)	...
Primary Progressive	2 (2.3%)	...
Duration of Diagnosis (years)	10.38 (8.37)	...
EDSS	2.74 (1.53)	...
Polypharmacy	28 (32.9%)	...
Using \geq 1 CNS medication	53 (62.4%)	...

Note. EDSS = Expanded Disability Status Scale; CNS = central nervous system

Impact of Polypharmacy

Descriptive data. Table 2 shows descriptive statistics for MS patients with polypharmacy and without polypharmacy. As can be seen, patients with polypharmacy were significantly older, had more disability as measured by EDSS, and had been diagnosed with MS for a longer duration in comparison to the patients without polypharmacy. As a result, these variables (age, EDSS, and duration of diagnosis) were included as covariates in subsequent analyses comparing the two MS groups. Contrary to expectations, depression scores on the BDI were not significantly different between the two groups; as such, depression was not used as a covariate in subsequent analyses.

Table 2

Descriptive Statistics for MS Patients with and without Polypharmacy

Variable	MS with Polypharmacy n=28		MS without Polypharmacy n=56		<i>t</i> (df)	<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
Age (years)	52.82	10.41	44.32	9.61	-3.73 (83)	< .001
Education (years)	15.04	2.06	14.85	1.89	-.411 (83)	.682
Diagnosis duration (years)	14.14	9.96	8.50	6.80	2.70 (39.995) ^a	.010
Disability (EDSS)	3.38	1.63	2.45	1.40	-2.72 (83)	.008
Depression (BDI)	2.89	2.97	2.61	2.77	-.426 (83)	.671

Note. EDSS = Expanded Disability Status Scale; BDI = Beck Depression Inventory

^a Equal variances not assumed.

Impact of polypharmacy on fatigue and perceived cognition. To examine differences on the self-report measures between MS patients with polypharmacy, MS patients without polypharmacy, and healthy controls, a MANCOVA was performed, controlling for age. Box's test of the assumption of equality of covariance matrices was significant ($p = .006$), however, indicating that the covariance matrices were not equal and thus violating the assumption of homogeneity. For this reason, a nonparametric version of MANCOVA was performed, using ranked variables in place of the raw data. Using this method, a significant effect of polypharmacy status on the self-report measures was found, $\chi^2(9, N = 103) = 41.72$, $p < .005$. The means and standard deviations for the self-report measures are displayed in Table 3. Follow-up ANCOVAs were performed to determine the nature of group differences on each of the self-report measures that were significant in the overall comparison.

Table 3

Comparison of Self-Report Measures between MS Patients with Polypharmacy, MS Patients without Polypharmacy, and Controls

Measure	MS with Polypharmacy		MS without Polypharmacy		Controls		F (df)	p
	M	SD	M	SD	M	SD		
PRMQ	46.11	9.95 _a	39.02	9.04 _b	33.20	7.08 _c	13.43 (2, 101)	<.001
PSDS	41.54	13.52 _a	32.71	10.84 _b	22.20	8.18 _c	14.61 (2, 101)	<.001
MFIS	12.04	3.82 _a	8.79	3.62 _b	4.45	2.54 _c	24.92 (2, 101)	<.001
DES	246.02	163.08	214.63	217.43	142.65	110.03	2.85 (2, 99)	.063

Note. Analyses performed using age as a covariate.

POLY = Polypharmacy; PRMQ = Prospective and Retrospective Memory Questionnaire; PSDS = Processing Speed Difficulties Scale; MFIS = Modified Fatigue Impact Scale; DES = Dissociative Experiences Scale.

Different lettered subscripts indicate significant differences at the $p < .05$ level.

Healthy controls versus MS patients, controlling for age. Both MS patients with and without polypharmacy reported more memory problems on the PRMQ than controls, $F(1, 45) = 31.30, p < .001$ and $F(1, 74) = 6.71, p < .05$, respectively. Similarly, MS patients with and without polypharmacy reported more processing speed difficulties on the PSDS, $F(1, 45) = 28.816, p < .001$ and $F(1, 74) = 18.46, p < .001$, and more fatigue on the MFIS, $F(1, 45) = 55.57, p < .001$ and $F(1, 74) = 24.92, p < .001$, when compared to controls.

MS patients with polypharmacy versus MS patients without polypharmacy. After controlling for age, EDSS, and disease duration, MS patients with polypharmacy reported more prospective and retrospective memory problems on the PRMQ than MS patients without polypharmacy, $F(1, 79) = 13.09, p = .001$. MS patients with polypharmacy also reported more processing speed difficulties on the PSDS than MS patients without polypharmacy, $F(1, 79) = 7.33, p < .01$, and significantly more fatigue on the MFIS, $F(1, 79) = 10.45, p < .01$.

Impact of polypharmacy on cognitive performance. To examine differences on the cognitive measures between MS patients with polypharmacy, MS patients without polypharmacy, and healthy controls, a multivariate analysis of covariance (MANCOVA) was performed, using age as a covariate. The overall multivariate test was significant, $F(12, 188) = 2.82, p = .001$. As shown in table 4, group differences were found on the MIST, Stroop, and SDMT, as well as a trend for the RAVLT delay trial, while no significant differences emerged for the RAVLT learning trial or the LNS task. In order to determine the nature of the group differences, follow-up ANCOVAs were performed for each of the cognitive measures that reached significance in the MANCOVA.

Table 4

Comparison of Cognitive Measures between MS Patients with Polypharmacy, MS Patients without Polypharmacy, and Controls

Measure	MS with Polypharmacy		MS without Polypharmacy		Controls		<i>F</i> (df)	<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
MIST	3.81	1.18 _a	5.02	1.05 _b	5.25	0.91 _b	9.74(2, 98)	<.001
Stroop	32.21	7.28 _a	35.82	6.19 _a	39.30	5.71 _b	4.57(2, 98)	.013
SDMT	45.67	12.01 _a	53.28	12.15 _a	60.25	8.64 _b	6.52(2, 98)	.002
LNS	9.19	2.24	9.80	2.36	10.65	2.32	1.62(2, 98)	.203
RAVLT delay	5.89	3.47	7.62	2.95	8.95	4.12	2.94(2, 98)	.058
RAVLT learning	24.56	6.15	25.64	6.16	28.30	6.05	1.71(2, 98)	.187

Note: Analyses performed using age as a covariate.

MIST = Memory for Intentions Screening Test; SDMT = Symbol Digit Modalities Test; LNS = Letter Number Sequencing Test; RAVLT = Rey Auditory Verbal Learning Task

Different lettered subscripts indicate significant differences at the $p < .05$ level.

MS patients versus healthy controls, controlling for age. MS patients with polypharmacy performed significantly worse on the MIST than healthy controls, $F(1, 45) = 15.87, p < .001$. MS patients with polypharmacy also performed worse than controls on the Stroop, $F(1, 45) = 8.55, p = .005$, and the SDMT, $F(1, 44) = 15.40, p < .001$. MS patients without polypharmacy also performed worse than controls on the Stroop, $F(1, 74) = 6.92, p =$

.01, and the SDMT, $F(1, 74) = 7.26, p = .009$. In contrast, MS patients without polypharmacy did not perform significantly worse than controls on the MIST, $F(1, 72) = 1.10, p = .297$.

MS patients with polypharmacy versus MS patients without polypharmacy. After controlling for age, EDSS, and disease duration, MS patients with polypharmacy performed worse on the MIST than patients without polypharmacy, $F(1, 77) = 12.67, p = .001$.

However, no significant differences were found between the two groups of MS patients on the Stroop, $F(1, 79) = .150, p = .70$, nor on the SDMT, $F(1, 78) = .774, p = .382$.

Impact of Medications with Unfavorable CNS Effects

Descriptive data. Table 5 shows descriptive data for MS patients using at least one CNS-detrimental medication and patients using no CNS-detrimental medications. As can be seen, patients using at least one CNS-detrimental drug were significantly older, had more disability as measured by EDSS, and had been diagnosed with MS for a longer duration in comparison to the patients without such medications. As a result, these variables (age, EDSS, and duration of diagnosis) were included as covariates in subsequent analyses comparing the two MS groups.

Table 5

Descriptive Statistics for MS Patients with and without CNS-Detrimental Medications

Variable	MS with CNS drugs (N=53)		MS without CNS drugs (N=31)		<i>t</i> (df)	<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
Age (years)	49.66	10.50	42.91	9.52	-2.97 (83)	< .01
Education (years)	15.08	2.10	14.64	1.63	-1.00 (83)	.32
Diagnosis duration (years)	13.06	8.87	5.81	4.82	4.85 (81.67) ^a	< .001
Disability (EDSS)	3.24	1.66	1.95	0.82	-4.75 (80.34) ^a	< .001
Depression (BDI)	2.45	2.92	3.13	2.65	1.06 (83)	.29

Note. EDSS = Expanded Disability Status Scale; BDI = Beck Depression Inventory.

^a Equal variances not assumed.

Impact of medications with unfavorable CNS effects on fatigue and perceived cognition. To examine differences on the self-report measures between MS patients using at least one CNS-detrimental medication, MS patients using no CNS-detrimental medications, and healthy controls, a MANCOVA was performed, using age as a covariate. As before, Box's test of the assumption of equality of covariance matrices was significant ($p = .006$), indicating that the covariance matrices are not equal and thus violating the assumption of homogeneity. For this reason, a nonparametric version of MANCOVA was performed. Using this method, a significant effect of CNS drug status on the self-report measures was found, $\chi^2(9, N = 103) = 43.96, p < .005$. The means and standard deviations for the self-report measures are displayed in Table 6. Follow-up ANCOVAs were performed to determine the

nature of group differences on each of the self-report measures that were significant in the overall comparison.

Table 6

Comparison of Self-Report Measures between MS Patients Using at Least One CNS-Detrimental Drug, MS Patients Using No CNS-Detrimental Drugs, and Controls

Measure	MS with CNS drugs		MS without CNS drugs		Controls		F (df)	p
	M	SD	M	SD	M	SD		
PRMQ	42.86	10.63 _a	39.16	8.50 _a	33.20	7.08 _b	7.76 (2, 99)	.001
PSDS	37.37	12.65 _a	34.00	11.76 _a	22.20	8.18 _b	11.39 (2, 99)	<.001
MFIS	10.96	3.95 _a	8.13	3.53 _b	4.45	2.54 _c	22.54 (2, 99)	<.001
DES	225.70	220.07 _a	175.66	156.80 _b	142.65	110.03 _b	5.34 (2, 99)	<.01

Note: Analyses performed using age as a covariate.

PRMQ = Prospective and Retrospective Memory Questionnaire; PSDS = Processing Speed Difficulties Scale; MFIS = Modified Fatigue Impact Scale; DES = Dissociative Experiences Scale.

Different lettered subscripts indicate significant differences at the $p < .05$ level.

MS patients versus healthy controls, controlling for age. MS patients using CNS-detrimental drugs reported significantly more memory problems on the PRMQ and more processing speed difficulties on the PSDS than did the controls, $F(1, 70) = 15.32, p < .001$, and $F(1, 70) = 20.83, p < .001$, respectively. MS patients using CNS-detrimental drugs also reported more fatigue on the MFIS and more dissociative experiences on the DES compared to controls, $F(1, 70) = 44.30, p < .001$, and $F(1, 68) = 7.95, p < .01$. MS patients without

CNS-detrimental medications also reported more memory problems than did the controls, $F(1, 49) = 7.24, p = .01$. Similarly, MS patients without CNS drugs reported more processing speed difficulties and more fatigue compared to controls, $F(1, 49) = 23.73, p < .001$, and $F(1, 49) = 16.69, p < .001$, respectively. No significant difference was found between these groups regarding dissociative experiences, $F(1, 49) = .715, p = .402$.

MS patients using at least one CNS-detrimental drug versus MS patients using no CNS-detrimental drugs. After controlling for age, EDSS, and disease duration, MS patients with at least one CNS drug reported significantly more fatigue and dissociative experiences than did patients without CNS drugs, $F(1, 79) = 7.45, p < .01$, and $F(1, 77) = 5.86, p < .05$, respectively. MS patients using at least one CNS drug reported more memory difficulties than did patients using no CNS-detrimental drugs, but this difference only trended towards significance, $F(1, 79) = 3.56, p = .063$. There was no significant difference between the two groups regarding self-reported processing speed difficulties, $F(1, 79) = .704, p = .40$.

Impact of medications with unfavorable CNS effects on cognitive performance.

To examine differences on the cognitive measures between MS patients using at least one CNS-detrimental medication, MS patients using no CNS-detrimental medications, and healthy controls, a MANCOVA was performed, using age as a covariate. The overall multivariate test was significant, $F(12, 188) = 1.84, p < .05$. As shown in table 7, group differences were found on the MIST, Stroop, and SDMT, while no significant differences emerged for the RAVLT learning trial, RAVLT delay trial, or LNS task. In order to determine the nature of the group differences, follow-up ANCOVAs were performed for each of the cognitive measures that reached significance in the MANCOVA.

Table 7

Comparison of Cognitive Measures between MS Patients Using at Least One CNS-Detrimental Drug, MS Patients Using No CNS-Detrimental Drugs, and Controls

Measure	MS with CNS drugs		MS without CNS drugs		Controls		<i>F</i> (df)	<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
MIST	4.38	1.14 _a	5.03	1.27	5.25	0.91 _b	3.29 (2, 98)	< .05
Stroop	33.33	6.33 _a	36.57	6.86 _a	39.30	5.71 _b	4.86 (2, 98)	.01
SDMT	47.06	10.58 _a	56.80	13.32	60.25	8.64 _b	9.73 (2, 98)	< .001
LNS	9.37	2.47	10.00	2.02	10.65	2.32	1.72 (2, 98)	.185
RAVLT delay	6.65	3.22	7.73	3.14	8.95	4.12	2.32 (2, 98)	.103
RAVLT learning	24.69	6.33	26.30	5.75	28.30	6.05	1.78 (2, 98)	.178

Note: Analyses performed using age as a covariate.

MIST = Memory for Intentions Screening Test; SDMT = Symbol Digit Modalities Test; LNS = Letter Number Sequencing Test; RAVLT = Rey Auditory Verbal Learning Task

Different lettered subscripts indicate significant differences at the $p < .05$ level.

MS patients versus healthy controls, controlling for age. MS patients using at least one CNS-detrimental drug performed significantly worse on the MIST compared to controls, $F(1, 69) = 6.84, p < .05$. MS patients using medications with unfavorable CNS effects also performed significantly worse on the Stroop, $F(1, 70) = 9.36, p < .01$, and the SDMT, $F(1, 70) = 18.57, p < .001$, compared to controls. MS patients without CNS-detrimental drugs performed worse than controls on the Stroop, $F(1, 49) = 5.23, p < .05$. No significant differences emerged between MS patients without CNS-detrimental medications and controls on the MIST, $F(1, 48) = 1.50, p = .226$, nor on the SDMT, $F(1, 48) = 2.38, p = .13$.

MS patients using at least one CNS-detrimental drug versus MS patients using no CNS-detrimental drugs. There were no significant differences between the two MS groups on the MIST, $F(1, 77) = .336, p = .564$, nor on the Stroop, $F(1, 79) = .001, p = .969$. Similarly, there was no significant difference between the MS groups on the SDMT, $F(1, 78) = 1.82, p = .182$.

Exploratory correlational analyses

Partial correlations were performed to examine the magnitude of the relationships between the number of daily medications and the cognitive and fatigue variables among the MS patients, controlling for age, level of disability, and duration of diagnosis. As shown in Table 8, the number of daily medications was positively associated with increased fatigue ($r = .440, p < .001$), self-reported prospective and retrospective memory problems ($r = .335, p < .01$), and self-reported processing speed difficulties ($r = .273, p < .05$). The number of daily medications was not significantly correlated with self-reported dissociative experiences, although a trend toward significance was found ($p = .059$). Patients taking more medications also performed more poorly on an objective measure of prospective memory ($r = -.255, p < .05$). As shown in Table 9, the number of daily medications was not related to objective cognitive performance on the Stroop, SDMT, LNS, RAVLT learning, or RAVLT delay trials.

Table 8

Summary of Partial Correlations among Number of Daily Medications and Self-Report Measures for MS Patients

	<i>#Meds</i>	<i>MFIS</i>	<i>PRMQ</i>	<i>PSDS</i>
MFIS	.440***			
PRMQ	.335**	.656***		
PSDS	.273*	.597***	.644***	
DES	.214	.509***	.539***	.535***

Note. Analyses performed using age, EDSS, and duration of diagnosis as covariates. #Meds = total number of daily medications, MFIS = Modified Fatigue Impact Scale, MIST = Memory for Intentions Screening Test, PRMQ = Prospective and Retrospective Memory Questionnaire, PSDS = Processing Speed Difficulties Scale, DES = Dissociative Experiences Scale.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 9

Summary of Partial Correlations among Number of Daily Medications and Objective Cognitive Measures for MS Patients

	<i>#Meds</i>	<i>Stroop</i>	<i>SDMT</i>	<i>MIST</i>	<i>LNS</i>	<i>RAVLT_{learning}</i>
Stroop	-.136					
SDMT	-.116	.578***				
MIST	-.255*	.178	.374***			
LNS	.046	.353**	.312**	.151		
RAVLT _{learning}	.070	.370***	.356***	.153	.468***	
RAVLT _{delay}	.008	.233*	.338**	.209	.311**	.783***

Note. Analyses performed using age, EDSS, and duration of diagnosis as covariates.

#Meds = total number of daily medications, SDMT = Symbol Digit Modalities Test, LNS = Letter Number Sequencing, RAVLT_{learning} = Rey Auditory Verbal Learning Test – sum of learning over first three trials, RAVLT_{delay} = Rey Auditory Verbal Learning Test – delay trial.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

CHAPTER 5

DISCUSSION

Polypharmacy is a growing concern in the medical community due the risk for adverse drug events (ADEs), which may involve drug-drug interactions, drug duplication, therapeutic duplication, or additive effects (Wright et al., 2012). Adverse reactions resulting from ADEs can vary from hypotension, confusion, and sedation to respiratory depression, bradycardia, and hypoxia (Wright et al., 2012). Polypharmacy has been most heavily researched in geriatric populations, where the use of multiple medications is most frequent (Fulton & Allen, 2005). Among older adults, polypharmacy has been linked to decreased functional ability, impaired cognitive functioning, and increased mortality (Alic, Pranjic, & Ramic, 2011; Eggermont, de Vries, & Scherder, 2009; Jyrkka et al., 2009a, 2009b; Jyrkka et al., 2011; Larson et al., 1987; Richardson et al., 2011).

Given the negative outcomes related to polypharmacy in older adults, it is worth exploring other patient groups that may experience unfavorable effects as a result of using multiple medications. It is ordinary for patients with MS to use an assortment of therapeutic drugs to manage their symptoms (Myers & Phillips, 1996). As suggested by Meador (1998), individuals with existing neurological damage, such as a traumatic brain injury, dementias, or MS, may have a greater risk of experiencing additional cognitive dysfunction as a result of medication effects. In fact, it has been suggested that drug side effects may impact neuropsychological test performance in patients with MS (Bruce, Thelen, & Westervelt, 2013). Despite this, there is a lack of knowledge regarding the effects of polypharmacy in MS. One study has reported that MS patients using one or more CNS-active medications experienced more fatigue and performed worse on measures of attention and processing

speed compared to MS patients using no medications with CNS effects. However, the sample was comprised of 52 patients using CNS-active drugs and only 18 patients without such medications, and the differences in the fatigue and cognitive measures disappeared after controlling for depression and physical disability (Oken et al., 2006). The difference in our results may be due to our larger sample size and use of different self-report and neurocognitive measures. To date, no researcher has examined how the number of daily medications (regardless of drug class) may impact fatigue and cognitive functioning in individuals with MS, using the standard definition of five or more drugs to indicate polypharmacy.

Summary of Findings

The primary objective of this study was to evaluate the associations between polypharmacy, objective cognitive performance, perceived cognitive difficulties, and fatigue in patients with MS. The secondary objective of this investigation was to assess the relationship between drugs with potentially detrimental CNS effects (e.g., opioids, benzodiazepines, etc.) and cognition and fatigue in MS patients, in order to further explore the concepts set forth by Oken and colleagues (2006).

Impact of polypharmacy. The first hypothesis, that MS patients with polypharmacy would exhibit significantly more problems with fatigue and cognition compared to MS patients without polypharmacy and healthy controls, was partially supported by the results. On the self-report measures, MS patients reported significantly more fatigue, prospective and retrospective memory difficulties, and processing speed difficulties compared to healthy controls. Furthermore, MS patients with polypharmacy reported significantly more impairment on these measures than the patients without polypharmacy. On the objective

cognitive measures, MS patients performed significantly worse than healthy controls on the Stroop, SDMT, and MIST. Comparing the two groups of MS patients, those with polypharmacy performed significantly worse on the MIST than patients without polypharmacy. There were no other significant differences in the objective measures between the two MS groups.

Impact of medications with detrimental CNS effects. The second hypothesis, that MS patients who use at least one medication with potentially unfavorable CNS effects would exhibit impairments in cognition and increased fatigue compared to MS patients without such drugs and healthy controls, was partially supported by the results. On the self-report measures, MS patients using at least one CNS-unfavorable medication reported significantly more fatigue, prospective and retrospective memory problems, processing speed difficulties, and more dissociative experiences, compared to healthy controls, after controlling for age. In comparison, MS patients using no such drugs also reported more problems than controls on the MFIS, PRMQ, and PSDS, after controlling for age. Between the two groups of MS patients, those using CNS-unfavorable drugs reported significantly more fatigue and dissociative experiences than patients without such drugs, even when controlling for age and disease variables. In contrast, self-reported memory and processing speed difficulties did not differ significantly between the two groups of patients. On the objective cognitive measures, MS patients using CNS-unfavorable drugs performed significantly worse than controls on the Stroop, SDMT, and MIST, after controlling for age. In comparison, MS patients who do not use such medications performed worse than controls only on the Stroop. However, MS patients who used CNS-unfavorable medications did not perform significantly worse on any of the objective cognitive measures compared to patients not taking such drugs.

Exploratory correlational analyses. An additional goal of the study was to determine whether the number of daily medications used by MS patients would be positively correlated with subjective fatigue, subjective cognitive impairment, and objective cognitive impairment. The results partially supported this premise. Patients' total number of medications was significantly related to increased fatigue, subjective memory problems, and self-reported processing speed difficulties. The number of medications was also correlated with objective prospective memory impairments; however, no other objective cognitive measures were significantly related to total medications.

Overall, the results from this study suggest that polypharmacy in patients with MS is associated with increased fatigue and subjective cognitive impairment. Interestingly, with the notable exception of prospective memory deficits, MS patients with polypharmacy did not perform significantly worse on objective measures of cognition when compared to MS patients without polypharmacy. Regarding medications with potentially unfavorable CNS effects, it was found that MS patients using at least one CNS-detrimental drug did not perform significantly worse on objective cognitive measures compared to MS patients using no such drugs. However, patients using CNS-detrimental drugs reported significantly more fatigue and dissociative experiences as compared to the other patients.

Potential Explanations for the Findings

There are a number of possible explanations for the link between polypharmacy and the self-report measures. For example, some personality variables, such as high neuroticism or trait anxiety, may lead a patient to perceive more health-related problems, and therefore use more medications, compared to patients who score low on these personality variables. Personality differences may account for varying harm-to-benefit ratios, with regard to

medication use. In other words, some patients may perceive greater harm from using medications, such as adverse side effects and financial cost. Meanwhile, other patients may feel that the benefits of medication outweigh the negative side effects.

It has also been reported that patients high in neuroticism or anxiety may overestimate their cognitive problems (Akbar, Honarmand, & Feinstein, 2011). Mood disturbances, including depression and anxiety, are suggested to correlate with core personality changes (Bruce & Lynch, 2011), and have also been linked with the overestimation of cognitive problems in MS (van der Hiele, Spliethoff-Kamminga, Ruimschotel, Middelkoop, & Visser, 2012). Alternatively, the combination of several medications could increase the risk of unfavorable side effects, such as lethargy or disorientation, which may lead patients to perceive cognitive problems like slowed information processing and executive dysfunction.

The association we found between polypharmacy and prospective memory performance was somewhat surprising, as no other objective cognitive measures were significantly related to polypharmacy in this sample. Prospective memory deficits have been documented in other MS samples (Bravin, Kinsella, Ong, & Vowels, 2000; McIntosh-Michaelis et al., 1991; Rendell et al., 2007), as well as other neurological patient groups, such as spina bifida (Dennis, Nelson, Jewell, & Fletcher, 2010), traumatic brain injury (Umeda, Kurosaki, Terasawa, Kato, & Miyahara, 2011), and dementia (van den Berg, Kant, & Postma, 2012). Some researchers propose that neurological damage in specific areas of the brain may lead to prospective memory impairment. Specifically, the lateral and medial prefrontal cortex (PFC) and Brodmann area 10 have been implicated in the maintenance and retrieval of prospective memory intentions (Benoit, Gilbert, Frith, & Burgess, 2012; Cona,

Arcara, Tarantino, & Bisiacchi, 2012; Momennejad & Haynes, 2012; Umeda et al., 2011). Additional evidence also suggests the involvement of the parietal (Rusted, Ruest, & Gray, 2011) and medial temporal lobes (Gordon, Shelton, Bugg, McDaniel, & Head, 2011).

Given the structural correlates of prospective memory, it is plausible that individuals with MS may have trouble remembering future intentions due to MS-related pathology in specific brain areas. Alternatively, the overall integrity of white matter tracts in MS patients has been linked with impaired access to consciousness (Reuter et al., 2009), which may affect the attentional component of prospective memory (Benoit et al., 2012; Okuda, Gilbert, Burgess, Frith, & Simons, 2011). Despite these potential mechanisms for prospective memory impairment in MS, it remains unclear why MS patients with polypharmacy would perform worse on prospective memory tasks relative to MS patients without polypharmacy.

While no published studies have explored the association between polypharmacy and prospective memory, there are some reports linking other drug use to prospective memory deficits. For instance, Hadjiefthyvoulou and colleagues (2011) reported that ecstasy/polydrug users performed significantly worse on both time- and event-based prospective memory tasks, compared to cannabis-only users and nondrug users, even after controlling for group differences in retrospective memory and executive function. Another study found that young adults who reported regular binge drinking exhibited impairments on time-based prospective memory tasks, but not event-based tasks, in comparison to non-binge drinkers (Heffernan & O'Neill, 2012). Additionally, prospective memory deficits were demonstrated in a sample of current cigarette smokers, as well as non-smokers who are exposed to second-hand smoke, compared to nonsmokers (Heffernan & O'Neill, 2013). Although the exact mechanisms underlying these deficits are unknown, several possible avenues have been suggested. One

possibility is that drug toxicity leads to neuronal damage (Ghosh, Mishra, Das, Kaushik, & Basu, 2009). It is also possible that the deleterious cardiovascular effects of alcohol, tobacco, and other drug use could lead to cardiovascular disease, which may be associated with impaired cognition (Llewellyn, Lang, Langa, Naughton, & Matthews, 2009; Ronksley, Brien, Turner, Mukamal, & Ghali, 2011; Shenouda, Carvalho, & Varner, 2010; Teo et al., 2006).

Lastly, a recent study suggests that lower white matter volume in the anterior PFC is correlated with prospective memory deficits, as well as patients' history of hypertension (Scullin et al., 2013). Furthermore, the investigators found a significant association between self-reported hypertension and performance on nonfocal prospective memory tasks. In the present study, 14 of the 86 participants with MS reported hypertension, with a majority of these patients using a medication to control their blood pressure. It is possible, therefore, that hypertension may have contributed to both polypharmacy and prospective memory deficits in this sample. This is purely speculative, however, as history of hypertension was not included as a covariate in statistical analyses. Future studies are encouraged to examine the potential relationship between hypertension and prospective memory deficits in MS.

Limitations

This study has a number of potential limitations. First, the construct of polypharmacy is inconsistently defined in the scientific literature. While we used the most common interpretation of the term, indicated by five or more daily medications (Fulton & Allen, 2005; Gnjidic et al., 2012; Haider et al., 2008; Jorgensen et al., 2001; Linjakumpu et al., 2002), this cutoff is somewhat arbitrary. Other researchers have defined polypharmacy as the concurrent administration of at least two medications (Hiroto, Asuka, & Teruhiko, 2005; Veehof, Stewart, Haaijer-Ruskamp, & Jong, 2000), three or more medications (Alic et al., 2011), four

or more medications (Bikowski, Ripsin, & Lorraine, 2001). Alternatively, some define polypharmacy as the use of more medications than are clinically indicated (Hanlon, Schmader, Ruby, & Weinberger, 2001), as opposed to a simple tally of medications. Although a cutoff of five medications to indicate polypharmacy has been shown to accurately estimate drug-related adverse effects (Gnjidic et al., 2012), future studies should consistently operationalize the construct of polypharmacy to ease comparison across studies and meta-analyses.

Second, adjustments were not made for varying dosage levels of medications or repeated daily drug administrations. For instance, if one subject took 10 milligrams of baclofen twice per day, and another subject took 20 milligrams of baclofen three times per day, then both participants were entered as having one daily baclofen prescription. It is possible that variations in dosage level and number of daily administrations exerted differential effects on fatigue and cognitive measures; however, given the limited number of participants and large number of different medications, this study did not have sufficient statistical power to fully examine the magnitude of these drug effects.

Another potential limitation of this study is the presence of factors interrelated with CNS-active drug use, such as pain and depression, which are also associated with cognitive changes. Depression is common in MS, and many of the participants in this study reported using an antidepressant medication. Interestingly, in this sample, the MS patients using at least one CNS-unfavorable medication reported slightly lower levels of depression on the BDI than the MS patients taking no CNS-unfavorable drugs (2.45 and 3.13, respectively), although this difference was not statistically significant. Therefore, it appears that depression plays a relatively small role in the impact of polypharmacy among this sample of patients.

Conclusions

The results of this study suggest that polypharmacy could play a role in fatigue and cognitive function among people with MS. Specifically, polypharmacy in this sample of MS patients was associated with increased fatigue and subjective cognitive impairments, as well as poorer performance on a prospective memory test. Additionally, patients with MS who use at least one medication with potentially unfavorable CNS effects reported significantly more fatigue and subjective cognitive problems than patients using no such drugs. Taken together, these results indicate that fatigue, a frequent and debilitating symptom in MS, may be exacerbated or augmented by the number and type of drugs used by the MS patient.

Currently, the Food and Drug Administration has not approved any drugs for the specific treatment of MS fatigue, although some medications, including amantadine and modafinil, are used for this purpose (MacAllister & Krupp, 2005). However, our results imply that it may be advantageous to consider a thoughtful and critical medication review and possible reduction in the number of daily medications for MS patients, rather than adding another drug to the regimen. It may also be beneficial to encourage patients to engage in empirically supported behavioral therapies to treat their symptoms when polypharmacy is a concern. This quasi-experimental study cannot directly address causality. In fact, given the ethical implications, no polypharmacy study can randomly assign patients to take five or more drugs. Nonetheless, the associations observed in this study suggest that a reduction in polypharmacy may be associated with reduced fatigue, improvements in perceived cognition, and prospective memory. From a research perspective, if a strong association exists between polypharmacy and adverse drug effects, there should be a greater effort to control for these factors when executing studies that investigate the correlates of cognition and fatigue.

Future longitudinal research with MS populations may wish to randomly assign patients to medication reviews aimed at reducing polypharmacy. If, following medication reduction, reduced fatigue and other improvements are observed, it may be possible to develop clinical guidelines that appropriately weight the costs and benefits of multiple medication administration in MS. Appropriately reduced medication regimens also have the potential to improve medication adherence and reduce medication costs, as has been reported in other patient populations (Kojima et al., 2012; Tsai et al., 2012). There is a dearth of polypharmacy research in the MS literature, and future studies should address this gap in knowledge. Additional information regarding the prevalence and correlates of polypharmacy in MS could inform future interventions to reduce detrimental medication effects in this population.

APPENDIX

Table A1

Classification of Medications Based on Central Nervous System Effects

Medication	Detrimental CNS effects	
	Yes	No
Alpha Blockers	X	
Anticholinergics	X	
Anticonvulsants	X	
Antidepressants		
SSRIs (e.g., sertraline, fluoxetine)		X
SNRIs (e.g., duloxetine; venlafaxine)		X
SARIs (e.g., trazodone)	X	
Tricyclics (e.g., amitriptyline)	X	
Antihistamines	X	
Antihypertensives	X	
Antimuscarinics	X	
Antispasmodics	X	
Atypical antipsychotics	X	
Benzodiazepines	X	
Diuretics	X	
Hypnotics	X	
Muscle relaxants	X	
Opiate analgesics	X	
Analeptics		X
Antacids		X
Antivirals		X
Antibiotics		X
Anti-diabetics		X
Anti-asthmatics		X
Biphosphonates		X
Disease Modifying Drugs / Immunomodulators		X
Hormones (e.g. estrogens, thyroid hormone)		X
Hypolipidemics		X
Migraine medication		X
NSAIDs		X
Phosphodiesterase (PDE) inhibitors		X

Note. SSRIs = serotonin reuptake inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; SARIs = serotonin antagonist and reuptake inhibitors

Table A2

Mechanism of Action and Adverse Effects Associated with CNS Drugs Used in the Sample[†]

<i>Drug Class</i>	<i>Examples</i>	<i>Indication(s)</i>	<i>Mechanism of Action</i>	<i>Adverse CNS Effects</i>
Anticholinergics	dicyclomine; oxybutynin; trospium	Neurogenic bladder	Muscarinic antagonist; inhibits muscarinic action of acetylcholine on smooth muscle, exerting direct antispasmodic effect	Dizziness, blurred vision, somnolence, asthenia, nervousness, cognitive changes, delirium
Anticonvulsants	gabapentin; lamotrigine; levetiracetam; phenytoin; topiramate; valproic acid	Seizure control, neuropathic pain, tremor, spasticity	Suspected to block voltage- sensitive Na ⁺ channels and modulate GABA receptors	Dizziness, somnolence, fatigue, asthenia, blurred vision, diplopia, nervousness, confusion, nystagmus
Antihistamines	meclizine; cetirizine; fexofenadine; loratadine	Nausea, vertigo, dizziness, allergies, hay fever	Inverse agonist of histamine; blocks the binding of histamine to its receptors	somnolence, fatigue

(Table continues)

<i>Drug Class</i>	<i>Examples</i>	<i>Indication(s)</i>	<i>Mechanism of Action</i>	<i>Adverse CNS Effects</i>
Antihypertensives				
Beta-blockers	atenolol; carvedilol; metoprolol	Hypertension	Suspected to antagonize catecholamines at peripheral adrenergic neuron sites; central effect of reduced sympathetic outflow to the periphery, suppresses renin activity	Dizziness (often due to hypotension), somnolence, lightheadedness, syncope, asthenia
Angiotensin II receptor agonists	propranolol; irbesartan; olmesartan	Hypertension, tremor	Blocks vasoconstrictor effects of angiotensin II by selectively binding to AT ₁ receptor	Dizziness (due to hypotension), fatigue
ACE inhibitors	lisinopril; ramipril	Hypertension	Decreases plasma angiotensin II, leading to decreased vasopressor activity and aldosterone secretion	Dizziness (due to hypotension), fatigue, asthenia
Ca ⁺ channel blockers	nifedipine; verapamil	Hypertension	Inhibits Ca ⁺ ion influx into cardiac muscle and smooth muscle	Dizziness (due to hypotension), fatigue, mood changes, nervousness, asthenia

(Table continues)

<i>Drug Class</i>	<i>Examples</i>	<i>Indication(s)</i>	<i>Mechanism of Action</i>	<i>Adverse CNS Effects</i>
Antimuscarinics	darifenacin; tolterodine	Neurogenic bladder	Muscarinic receptor antagonist: inhibits cholinergic muscarinic receptors to mediate contractions of urinary bladder smooth muscle	Dizziness, somnolence, fatigue
Antispasmodics	baclofen	Spasticity, overactive bladder	GABA analog, suspected to inhibit both monosynaptic and polysynaptic reflexes at spinal level	Dizziness, somnolence, asthenia, fatigue, confusion, daytime sedation
Atypical antipsychotics	aripiprazole	Psychiatric mood disorder	Partial agonist of D ₂ receptor; partial agonist of 5-HT _{1A} receptor; antagonist of 5-HT _{2A} receptor	Blurred vision, fatigue, somnolence, dizziness, anxiety, insomnia, extrapyramidal symptoms
Benzodiazepines	alprazolam; clonazepam; diazepam	Spasticity, tremor, anxiety	Suspected to enhance GABA activity, which decreases excitability of neurons	Somnolence, lightheadedness, confusion, blurred vision, asthenia, nervousness

(Table continues)

<i>Drug Class</i>	<i>Examples</i>	<i>Indication(s)</i>	<i>Mechanism of Action</i>	<i>Adverse CNS Effects</i>
Diuretics	furosemide; hydrochlorothiazide; spironolactone	Hypertension, edema	Alters renal tubular mechanism for electrolyte reabsorption; inhibits absorption of Na ⁺ and Cl ⁻ ions, thereby leading to their excretion	Asthenia, dizziness (often due to hypotension), confusion, ataxia
Hypnotics	eszopiclone; zolpidem	Sleep aids, muscle relaxation	Suspected to interact with GABA-receptor complexes located near to or allosterically coupled to benzodiazepine receptors	Somnolence, dizziness, lethargy, altered cognition, impaired psychomotor function
Muscle relaxants	metaxalone; methocarbamol; tizanidine	Spasticity, muscle strain	Centrally-acting α_2 -adrenergic agonist; increases presynaptic inhibition of motor neurons	Somnolence, dizziness, asthenia, lightheadedness, blurred vision, syncope
Opiate analgesics	hydrocodone; methadone; tramadol	Pain control	Acts on opiate receptors in CNS; tramadol is suspected to bind parent and M1 metabolite to μ -opioid receptors	Dizziness, lightheadedness, sedation, somnolence, asthenia

(Table continues)

<i>Drug Class</i>	<i>Examples</i>	<i>Indication(s)</i>	<i>Mechanism of Action</i>	<i>Adverse CNS Effects</i>
Serotonin antagonist and reuptake inhibitors (SARIs)	trazodone	Depression, pain control, tremor, anxiety	Selective inhibition of neuronal uptake of serotonin and antagonism at 5-HT _{2A/2C} receptors	Somnolence, nervousness, blurred vision
Tricyclic antidepressants	amitriptyline	Neuropathic pain, depression, anxiety	Inhibits membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons	Blurred vision, stroke, seizure

Note. Na⁺ = sodium ion; GABA = gamma-aminobutyric acid; AT₁ = angiotensin II receptor type 1; Ca⁺ = calcium ion; D₂ = dopamine receptor subtype 2; α₂ = noradrenergic (norepinephrine) receptor; 5-HT_{1A/2A/2C} = serotonin receptor subtypes 1A, 2A, and 2C; Cl⁻ = chloride ion

† Information obtained from www.pdr.net (PDR Network, 2013).

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VITA

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