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"Taming the beast": Exploring the lived experience of relapsing remitting multiple sclerosis using a life history approach

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CHAPTER 2: OVERVIEW OF MULTIPLE SCLEROSIS

Following on from the brief introduction of MS in the previous chapter, chapter 2 will provide a more comprehensive overview of MS. This is primarily to support situating the context of the study as people living with an unpredictable and potentially serious threat to health and wellbeing but also to give an understanding of the many possible symptoms of RRMS and the specific issues that relate to living with the disease. RRMS has a great variability of possible presentations and disease courses, as well as being a complex disease to clinically diagnose and manage. Having an understanding of the overall picture of MS and more specifically RRMS will help the reader to appreciate the impact of the themes and sub-themes of the study findings and to realise the overall significance of the research in terms of potentially improving clinical care for PwRRMS in the future.

What is MS?

MS is a disease of the central nervous system (CNS) affecting the brain, spinal cord and optic nerves. MS is a progressive inflammatory disorder in which there is damage to key components of the nerve cells, namely myelin and axons (Compston & Coles, 2008). The pathological processes involved in MS are immune mediated and directed against the myelin sheath, the protective covering of the axons, termed *demyelination* (Calabresi, 2004). More recently it has become apparent that grey matter disease occurs early in the disease process, causing additional inflammation and neurodegeneration and possibly playing a role in physical and cognitive disability (Calabrese et al., 2015).

As a result of demyelination and the subsequent healing process, sclerotic plaques (scars) develop in multiple areas of the CNS. This pattern needs to occur more than once to fulfil the diagnosis of MS - *multiple* sclerotic lesions in *multiple* locations. However, over time, the disease becomes one of chronic neurodegeneration rather than acute inflammation, with progressive accumulation of disability due to nerve loss (Compston & Coles, 2008). The impaired nerve conduction, resulting from

demyelination and axonal loss, leads to many of the signs and symptoms of MS. The course of MS is highly variable and patients may develop irreversible disability, with MS remaining a major cause of disability in young adults (Brownlee et al., 2016). MS remains incurable, although recent breakthroughs in understanding MS and more targeted treatments are resulting in a brighter future for people recently diagnosed with the disease.

Clinically Isolated Syndrome (CIS)

Most cases of MS present with an acute *first* episode, known as the clinically isolated syndrome (CIS) (Compston & Coles, 2008). Until recently, a diagnosis of MS was not able to be made at the time of CIS, even if highly suspected, because there needed to be two clinical relapses more than 30 days apart to meet the diagnostic guidelines of a *multiple* relapsing MS course (Poser 1983; McDonald et al., 2001; Polman et al., 2005). This situation was often frightening for many patients after suffering a first relapse, with no clear answers and just a "wait and see" approach. In recent years, it has become possible with the revised diagnostic guidelines to diagnose MS after one CIS, if the magnetic resonance imaging (MRI) and other testing meets certain criteria to demonstrate multiple relapses (Polman et al.,,2011; Thompson, Banwell, & Barkof, 2018). Internationally, the currently used criteria for diagnosing MS are known as the 2017 McDonald criteria (Thompson et al., 2018).

Once the McDonald criteria have been met and the diagnosis of MS has been confirmed, there are three clinical course descriptions (phenotypes) of MS that will categorise the disease and thereby guide future treatment, prognostication and management strategies (Lublin et al., 2014). These are relapsing remitting MS, secondary progressive MS and primary progressive MS. Educating patients and families about the differences between these phenotypes is essential, as they are very different disease courses each with different treatment options.

Relapsing Remitting MS (RRMS)

The majority of people diagnosed with MS (up to 85%) begin with a diagnosis of RRMS (Milo & Miller, 2014; Brownlee et al., 2016). A relapse is defined as "patient reported or objectively observed events typical of an acute inflammatory event in the

central nervous system (CNS), current or historical, with duration of at least 24 hours, in the absence of fever or infection" (Polman et al., 2011, p.293). Relapses are also referred to as "exacerbations", "attacks" and "flare-ups" but the term relapse will be used throughout this thesis for clarity and consistency. New relapses occur erratically but seldom occur more than one to two times per year (Compston & Coles, 2008). Typically, people recover from a relapse and return to baseline (before the relapse) function over a period of four to eight weeks, but recovery can be uncertain, variable and incomplete (Sorensen, 2014). Additionally, although it may appear that physical function is returned following a relapse, there is still a measurable and sustained effect on disability from relapses (Lublin et al., 2003). Relapse symptoms are generally considered to resolve over time, even if not treated (Ross, Halper, & Harris, 2012). However, if the relapse symptoms are bothersome or affecting function, treatment may be considered to speed up the process of recovery, usually involving a short course of high dose corticosteroids to reduce the acute inflammation (Bevan & Gefland, 2015; Kalincik, 2015; Yamasaki et al., 2016). Relapses can be a significant physical, emotional and economic burden with the reduction of relapses by using disease modifying therapy (DMT) an important goal of treatment in order to reduce future neurological disability (Kalincik, 2015). The forms of DMT available to treat RRMS and their implications will be discussed later in this chapter.

At present there is no tool or test that can advise what the future clinical course of RRMS will be for an individual, adding to the uncertainty at the time of diagnosis (Bergamaschi et al., 2015) where no specific information on prognosis can be given. However, there are prognostic risk factors which can provide some guidance, including a better prognostic outlook for PwRRMS who are female, experiencing sensory rather than motor relapses and showing minimal burden of disease on imaging (Weinshenker, 1995). There are groups of people with RRMS who experience very few symptoms and little clinical activity and yet others have highly active clinical and radiological disease (Hum, Lapierre, Scott, Duquette, & Mayo, 2017). MS progression can be so variable that there was a time when it was thought that no common disease course existed and that each patient followed a unique path (Minderhoud, van der Hoeven, & Prange, 1988).

Secondary Progressive MS (SPMS)

Over time, recovery from relapses in RRMS is incomplete and accumulation of disability begins (Compston & Coles, 2008). SPMS is diagnosed retrospectively by a history of gradual worsening, after an initial relapsing course, with or without acute relapses during the progressive course (Lublin et al., 2014). There are no clear criteria to determine exactly when this transition occurs, it can be an unpredictable and uncertain period of time for PwRRMS (Bergamaschi et al., 2015) and also for their HCPs. The natural history data on the course of MS suggests that on average, SPMS occurs about 19 years after RRMS onset, with PwSPMS taking an average of 20 years to progress to using a walking stick and 30 years for wheelchair dependance (Vukusic & Confaveux, 2006). Reaching SPMS at a younger age and with only a short RRMS course has also been asssociated with a more rapid disease progression (Tremlett, Zhao & Devonshire, 2008).

Primary Progressive MS (PPMS)

PPMS is a separate clinical phenotype affecting 10-15% of people diagnosed with MS (Milo & Miller, 2014). PPMS is progressive in nature from disease onset with gradual worsening of neurological function and no relapses occurring (Compston & Coles, 2002). It has been hypothesised that PPMS represents a distinct, non-inflammatory form of MS (Lassmann, van Horssen, & Mahad, 2012), which may explain why the traditional DMTs (which are effective in RRMS) do not alter the disease course in PPMS. However, there has also been recent literature to suggest that in PPMS there may be some inflammatory activity, but it is different in nature to RRMS and SPMS and features axonal destruction and eventually brain atrophy (Mahad, Trapp, & Lasmann, 2015). Compared with RRMS, people with PPMS are older at onset and a higher proportion are men (Lassmann, van Horssen, & Mahad, 2012). There has recently been a breakthrough in a new treatment for PPMS with Ocrelizumab, a CD-20 monoclonal antibody,leading to depletion of B-cells and demonstrating effectiveness in PPMS by slowing disease progression (Hauser, 2015). Ocrelizumab has very recently been approved for use in Australia and internationally.

New classifications for MS

There has recently been a suggestion to reclassify the phenotypes of MS, taking into account disease activity; reclassifying PwMS as experiencing either a *relapsing* or *progressive* path and with either *active* or *inactive* disease and either *progression* or *non-progression* (Lublin et al., 2014). However, this has not universally been adopted at present, so reference to the original phenotypes outlined above will be used throughout this thesis.

Natural History of MS

Much is known about the natural history of MS, mainly because there were no treatments or disease modifying drugs until the 1990's (Jacobs et al.,1996). The natural history pattern is highly variable. The seminal natural history data from Weinshenker (1994) suggests that at 15 years from disease onset, 50% of patients are disabled to the point of needing a walking stick to ambulate. Additionally, an early age at onset, female sex, relapsing-remitting course at onset, optic neuritis or sensory symptoms and relatively few attacks in the first two years are associated with a more favourable course (Weinshenker, 1994). Conversely, patients with the greatest risk of disability are those with PPMS or RRMS patients who are older at onset, have pyramidal or cerebellar involvement, and who have frequent or prolonged attacks with incomplete recovery. The biological basis for the variation in the course of MS is poorly understood.

Epidemiology

In many countries MS is the leading cause of non-traumatic neurologic disability in young adults (Browne et al., 2014). The Australian Bureau of Statistics (ABS) estimate a total of 23,700 people in Australia to be living with MS (ABS, 2009). However, more recent data from Multiple Sclerosis Research Australia (MSRA) suggests this number may now be as high as 25,600, with an average of more than 10 people being diagnosed in Australia every week (MSRA, 2018). The increasing incidence and prevalence of MS over the last five decades (Pugliatti et al., 2006; Koch-Henricksen & Sorensen, 2010) is concerning and requires continued research

to better understand the potential environmental factors impacting on the development of the disease.

Interestingly, the prevalence of MS has a female preponderance with women almost three times more likely than men to develop the disease (Koch-Henriksen & Sorensen, 2010). RRMS can occur at any age, but the most common age for diagnosis is as a young adult between 18 and 40 years, with a mean age of 30 years (Compston & Coles, 2008). However, paediatric MS occurs in about 5% of cases with onset before the age of 18 years (Lulu, Graves, & Waubant, 2016) and is more prevalent in adolescents than younger children (Waldman et al., 2016).

Causes of MS

The cause of MS is unknown, however there are several clues about how MS begins (Spencer & Karceski, 2015). It is thought that MS is caused by a complex interplay between the immune system and environmental factors (Compston & Coles, 2008). It seems unlikely that MS results from a single causative event, but rather the disease develops in a genetically susceptible population as a result of environmental exposures (Ramagopalan & Sadovnick, 2011). Exposure to environmental risk factors in MS is thought to occur before the age of 15 years (Belbasis, Belbu, Evanelou, Ionnidis, & Tzoulaki, 2015). The risk factors thought to be associated with an increased risk of MS include Epstein-Barr and other viral and bacterial infections, vitamin D levels, geographical location/latitude gradient (the closer to the poles, the greater the prevalence of MS), cigarette smoke exposure, and certain human genotypes (Banwell, Bar-Or, Giovannoni, Dale, & Tardieu, 2011; Sellner et al., 2011) as well as obesity, gut microbiota and pregnancy exposures (Belbasis, Belbu, Evangelou, Ionnidis, & Tzoulaki, 2015). The infection exposure theory is currently thought to originate in childhood, where antibodies are formed against an infectious agent (an as yet identified virus or bacteria) and for reasons that are unknown, these antibodies attach to a protein in the myelin coating of the axons resulting in the body becoming confused and destroying the protective myelin (Spencer & Karceski, 2015).

MS has a familial recurrence rate of about 5% for siblings and about 2% for children and parents (Compston & Coles, 2008), suggesting genetic links but not heritability of the disease, with most PwMS having no affected relative (Coyle, 2016). Recent genetic research has accelerated the understanding of genetic MS theories with the identification of non-human leukocyte antigen (HLA) risk genes that are related to immune function (Waubant et al., 2016), opening exciting new areas of hope for answering questions about the causes of MS in the future.

Diagnosing MS

The diagnosis of MS is based on neurological signs and symptoms and is primarily a clinical diagnosis, assisted by specific investigations (Brownlee et al., 2016). Often there are significant delays before a person with symptoms suggestive of MS sees a neurologist and receives a diagnosis (Giovannoni et al., 2016). There are several reasons for this delay including lack of recognition of symptoms by the person, the family doctor not referring on, lack of available neurology care and appointments and symptoms being both vague and intermittent in nature.

In most PwRRMS, clinical manifestations (the symptoms) reflect the area of demyelination in the CNS and indicate the involvement of motor, sensory, visual, and autonomic systems, but many other symptoms and signs can occur (Compston & Coles, 2008). Adding to the difficulties with diagnosis, very few clinical features are disease-specific and there is no pathognomonic test for MS. Specifically, there is not one symptom, sign, or paraclinical result that provides an unfailingly accurate diagnosis of MS (Giesser, 2011). This can be a time of extreme frustration for patients as often the diagnosis involves many tests and investigations and can sometimes not be definitive, and in some cases, not definitive for many years.

Over the last four decades, certain criteria have been developed to help guide the diagnosis of MS, beginning with Poser et al. (1983) and followed by the "McDonald criteria" (McDonald et al., 2001), which incorporated the MRI scan for the first time. The McDonald criteria were updated in 2005 (Polman et al., 2005), again in 2010 (Polman et al., 2011) and more recently in 2017 (Thompson et al., 2018) to reflect changes in MS knowledge and practice. The most recent changes have made an

important impact, allowing for an earlier diagnosis of MS, leading to more rapid treatment initiation and reducing the risk of disease progression (Mantero, Abate, Balgera, La Mantia, & Salmaggi, 2018). This has led to an increase in MS cases being diagnosed but still requires careful assessment to prevent misdiagnosis and mistreatments (Mantero et al., 2018). However, this can also create significant emotional and coping issues as people can be diagnosed with RRMS in just one visit to the neurologist, and then also face difficult and complex treatment decisions simultaneously.

Investigations used to diagnose MS

In addition to neurological and clinical examinations, diagnosing MS often depends on excluding other disorders that can mimic MS (Filippi et al., 2016). Some of these investigations include the MRI scan, neurophysiological tests such as evoked potentials and extensive blood tests. A spinal tap or lumbar puncture (LP) can also be performed to obtain cerebrospinal fluid (CSF) for examination to assess for the evidence of oligoclonal bands, which can assist in confirming an MS diagnosis. Most of the investigations are not painful but can be uncomfortable at times (MRI, LP, blood tests), difficult (LP) or induce feelings of claustrophobia (MRI).

The Expanded Disability Status Scale

The Expanded Disability Status Scale (EDSS) is used to quantify the degree of MS related disability in individual patients (Kurtze, 1955; 1983). Many studies show that MS relapses can leave permanent neurological deficits and play a role in disability accumulation (Goodin et al., 2016). The EDSS aims to measure the neurological function and provide a score to reflect neurological deficits. A clinical examination of eight functional systems impacted by the CNS (pyramidal, cerebellar, brain stem, sensory, bowel/bladder, visual, cerebral and other) results in individual scores which are compiled together with ambulatory data to form a total score, the EDSS. The final score ranges between 0 and 10, with 0.5 measurements between each level. A score of 0 indicates no neurological impairment, a score of 1.0 indicates mild disability in a single area, a score of 4.0 indicates that a person is fully ambulatory

but accruing significant disability in several functional areas, a score of 6.0 indicates assistance required to ambulate with a unilateral walking assistance, 6.5 bilateral walking assistance or walker, a score of 7.0 indicates wheelchair dependence and a score of 9.0 indicates confinement to bed. An EDSS score of 10 relates to death from MS.

Common symptoms in MS

The initial presentation of MS varies according to both the location and size of lesions and the type of onset (relapsing or progressive onset) (Brownlee et al., 2016). Common symptoms in MS can greatly affect quality of life (QOL) and rarely occur in isolation (Crayton & Rossman, 2006; Newland, Thomas, Riley, Flick, & Fearing, 2012). These symptoms include fatigue, depression, anxiety, cognition issues, bladder and bowel dysfunction, sexual dysfunction, pain, spasticity, motor weakness, sensory dysfunction, visual disturbances, ataxia and gait disturbances. Symptoms usually result directly from nerve conduction issues secondary to demyelination, either in response to an acute relapse, or as long-term consequence of previous demyelination and axonal loss. Additionally, many of these symptoms are not immediately obvious to others and are described as "hidden" or "invisible" symptoms of MS, which can lead to possible stigmatisation or poor understanding by others who do not have the disease (Joachim & Acorn, 2000).

Symptom management in MS is an integral part of its care, with accurate assessment and management providing increased quality of life (Ben-Zacharia, 2011). It has been suggested that MS-related fatigue is different to normal fatigue due to its severity and the ability to significantly impact upon daily activities (Newton, Griffiths, & Soundy, 2016), being complex, multidimensional and poorly understood (Smith, Hale, Olson, Baxter, & Schneiders, 2013). There are two symptoms, not diagnostic of, but often peculiar to, demyelination in MS. These are L'hermittes sign, which is an electric shock-like feeling when flexing the neck forward and is caused by inflammation in the spinal cord (Al-Araji & Oger, 2005). The second is Uhthoff's phenomena, MS symptoms which can be worsened or triggered by factors such as the menstrual period, exercise, infection, fever and stress and refers to symptoms

coming on paroxysmally and being reversible (Frohman et al., 2013). "Pseudo-relapses" can occur in RRMS and describe fatigue occurring in isolation or a transient fever-related worsening of MS symptoms (Polman et al., 2011).

Aside from the highly variable disease state and multitude of possible neurological symptoms, MS can also cause numerous secondary and tertiary effects. Issues may develop in highly personal areas of intimacy and sexuality, relationships and employment. MS often causes challenges for people coping with the disease and the associated changes in life (Rommer, Koenig, Suhnel, & Zettl, 2015).

MS and mental health issues

MS is often diagnosed at an exciting time of life, when young adults are graduating from school or university, getting married, starting a family or advancing a career, MS therefore has the potential to cause significant emotional stress in the lives of people diagnosed with the disease. As a result of the current shortened diagnostic workup, people with RRMS can be rapidly confronted with a disease of uncertain prognosis that requires complex treatment decisions (Solari et al., 2014). This can also be at a time of great vulnerability when PwRRMS could be ill-equipped to make these decisions due to recent high dose steroid treatments, feelings of stress and worry, other mental health issues, confusion over the meaning of the disease and the wealth and complexity of available information and resources. Anxiety and depression in particular have both been associated with less adherence to medication, increased risk of relapses, cognitive impairment, increased use of health resources, mortality, fatigue and pain in PwMS (de Jong & Uitdehaag, 2018). An additional area of concern is the rate of suicide in people living with MS, which is up to seven times greater than the general population (Pompili, 2012).

Anxiety

It is not surprising that the unpredictable nature of RRMS, specifically with respect to relapses and potential for disability, leads to anxiety (Morrow, 2018). Anxiety is a diagnosable mental health illness under the Diagnostic and Statistical Manual of Mental Disorders (DSM-V®) with a variety of criteria and specific anxiety disorders

(APA, 2013). Several studies exploring anxiety in MS have shown that anxiety is more prevalent in the MS population than in the general population (Feinstein, Magalhaes, Richard, Audet, & Moore, 2014) and may be as high as 36% in PwMS (Hoang, Laursen, Stenager, & Stenager, 2016). A large cohort study (n=5084) of MS patients matched with a control population, has reported that during both the pre and post diagnostic period, MS patients had an increased risk of anxiety and medication usage when compared to the general population (Hoang et al., 2016). In RRMS, anxiety may be severe and prolonged due to the uncertain nature of the disease, in terms of relapses, symptoms and disease progression (Janssens et al., 2004). Furthermore, anxiety has been strongly associated with lower QOL scores across all levels of illness severity, from mild impairment to severe (Ionescu et al., 2012). Anxiety is more prevalent in females than males in PwMS (Theaudin, Romero, & Feinstein, 2016) and needs regular assessment and evaluation. There is also a higher likelihood of alcohol use, substance abuse and smoking associated with anxiety in PwMS (Marrie et al., 2015).

Anxiety has also been identified as being significantly associated with low levels of disease acceptance and mindfulness in MS (Pakenham & Samios, 2013), which may have direct consequences on adherence to DMTs and to MS wellness prescriptions. Anxiety is most highly associated with depression, low self-efficacy, stress, emotion focused coping, pain, fatigue and QOL, factors that may be amenable to intervention if identified and actioned by MS HCPs (Butler, Matcham, & Chalder, 2016).

Depression

As with anxiety disorders, depressive disorders are a diagnosable mental health illness under the DSM-V® with listed criteria including depressed mood, loss of interest and enjoyment in usual activities, reduced energy, reduced self esteem and confidence, ideas of guilt and unworthiness, pessimistic thoughts, disturbed sleep and appetite and ideas of self harm (APA, 2013). For people with MS the lifetime prevalence rate of a depressive disorder has been reported as greater than 50% (Hoang et al., 2016) and is three times higher than the general population (Kessler et al., 2012; Patten, Beck, Williams, Barbui, & Metz, 2003). Depression in MS is still

undertreated and under-recognised and most importantly, depression can be fatal (Feinstein, 2011; Newsome et al., 2017)

A multitude of aetiologic factors contribute to depression in MS, including biological (lesion burden, location of lesions and brain atrophy) as well as the stresses, losses and threats that accompany living with an unpredictable and potentially disabling disease (Patten et al., 2003). Depression in MS is extremely complex and complicated by other factors such as fatigue, cognition and physical impairment, which can also mimic depression and prevent accurate diagnosis (Gunzler et al., 2015). Turner and Alschuler (2018) suggest that depressed mood and MS symptoms such as fatigue, cognition and pain have a bidirectional relationship, each causing the other to be worse. Depression in MS possibly has a different pathophysiology to the general population and has been described as chronic rather than episodic in nature (Koch et al., 2015). Additionally, depressive syndromes occur with significant frequency across the natural history of MS, including patients with very mild forms of MS, and do not correlate well with the severity of neurologic disability (Perez, Gonzales, & Lazaro, 2015).

Treatments for RRMS

Disease modifying treatments for MS

There have been many recent developments in treatments for RRMS, however a cure for the disease remains elusive. The immune dysregulation in the development of MS leads to a cascade of events resulting in inflammation and axonal degeneration in the CNS (Grigoriadis & van Pesch, 2015). The DMTs act to interrupt this cascade at varying points of the process. The goal of the DMT is to delay the accumulation of disability and to delay transition to the more progressive and disabling SPMS (Liu et al., 2016). The occurrence of a relapse on a DMT is usually considered an indication of breakthrough disease and suboptimal response (Liu et al., 2016) and often results in a "switch" of DMT to another therapy, usually to a more efficacious medication (Bevan & Gelfand, 2015). However, as no current DMT completely eradicates disease activity, there is much debate currently about what constitutes breakthrough

disease and what the primary aim of treatment is; as treatment goals move and monitoring of outcomes is more active (Giovannoni et al., 2015).

In the past 20 years RRMS has been transformed from a disease of relative hopelessness, with few, if any, treatment options to one of optimism and robust therapeutic promise (Ross & Thrower, 2010). The approval of immune modifying medications for RRMS is often cited as a major advance in our understanding, however many questions still remain unanswered (Stüve & Racke, 2016). Whilst the number of DMTs are rapidly increasing, there is still need to define which patients will respond to which drug and who is at higher risk of side effects (Stuve & Racke, 2016). The option of individualised optimal treatment is complicated because of the unpredictable natural behavior of the disease, the different phenotypes and stages, the diversity of different therapies, and the serious and sometimes life-threatening side-effects of some of the treatments (Rio, Comabella, & Montalban, 2011).

With advances in DMTs, survival in RRMS has increased and a slower accumulation of disability has resulted (Tremlett, Zhao, Rieckmann, & Hutchinson, 2010) with the natural history of the disease shown to be altered in randomized clinical trials (Wingerchuk & Carter, 2014). Treatment options for the disease are most effective during the relapsing remitting phase and are recommended to start early after diagnosis for the best clinical outcomes (Broadley et al., 2015; Kavaliunas et al., 2017). Australia is in a fortunate situation in terms of registered and government supported programs for DMTs to treat RRMS. There are set criteria to follow in order to gain Pharmaceutical Benefits Scheme (PBS) approval, but once these criteria are met, patients can be prescribed a range of DMTs, benefitting from an individualised approach to choose the DMT most appropriate for their level of disease activity and based on pathpohysiology and illness patterns. The cost of these medications is high, but the DMTs are made available to patients in Australia at greatly subsidised rates. All available medications have been tested clinically for safety and efficacy in large, multicentre clinical trials in people with RRMS. Many other countries (currently such as Great Britain) have restrictions on which medications may be used at which stage of the disease or have regulations on which medications need to be used as first, second or third line therapy (Giovannoni et al.,

2016) or other countries (such as the United States) need to rely on approval from insurance companies to begin a certain DMT (Parise et al., 2013).

There are currently 12 DMTs approved to treat RRMS in Australia; the injectable medications which the patient learns to self-inject (four forms of interferon beta, two forms of glatiramer acetate) the oral medications (fingolimod, dimethyl fumarate and teriflunomide) and the intravenous monoclonal antibody medications (natalizumab, alemtuzumab and ocrelizumab). A current list of DMTs approved in Australia is listed in Table 1. The many options for treatment can be complex and challenging to negotiate, however there are suggested guidelines that can be followed to assist in choosing the most appropriate DMT for patients with RRMS (Broadley et al., 2014a; Finkelsztejn, 2014).

Table 1. *Currently approved and marketed DMTs for RRMS in Australia*

Generic name	Trade name	Mode of delivery	Frequency of dosing	Common side effects or serious side effects
Interferon beta-1b	Betaferon®	subcutaneous injection	every other day	influenza-like symptoms (fever, chills), injection site reactions, depression
Interferon beta -1a	Rebif®	subcutaneous injection	three times a week	as above
Interferon beta- 1a	Avonex®	Intramuscular injection	weekly	as above
Interferon beta- 1a-pegylated	Plegridy®	subcutaneous injection	fortnightly	as above
glatiramer acetate	Copaxone®	subcutaneous injection	daily or three times/week	injection site reactions, lipoatrophy "immediate post injection reaction"
Teriflunomide	Aubagio®	Oral	daily	liver enzyme elevations, hair thinning, nausea
Dimethyl fumarate	Tecfidera®	Oral	twice daily	gastrointestinal disturbances, flushing, rare PML
fingolimod	Gilenya®	Oral	daily	first-dose cardiac effects, infections, macular oedema, liver enzyme elevations, skin malignancies, rare PML
Natalizumab	Tysabri®	Intravenous infusion	Every 4 weeks	infusion related side effects, variable risk of PML
Alemtuzumab	Lemtrada®	Intravenous infusion cycle	Annually x 2 years	infusion related side effects, autoimmune side effects (thyroid, blood and renal)
Ocrelizumab	Ocrevus®	Intravenous infusion	6 monthly	infusion related side effects, ?malignancies

All of the DMTs have side effects associated with their use, some of which (such as injection site reactions and intermittent mild diarrhoea) can be easily managed. Some of the newer treatments (the monoclonal antibodies) are more efficacious than the injectable therapies, reducing relapse rates by 50-70% compared to approximately 30% for injectables (Kalincik et al., 2017). However, they do possess significant

additional safety concerns. The newer DMTs require specific monitoring for adverse events, some of which can be fatal if not recognised early (Finkelsztejn, 2014). The added pressures of greater efficacy balanced with an increased side effect profile can cause significant stress and emotional burden for PwRRMS. Additionally, factors such as cognition issues, tolerance for side effects, cost and fatigue play havoc with adherence to treatments (Kopke, Solari, Khan, Heeson, & Giordano, 2014).

Some of the more serious side effects related to DMTs came up frequently in the data collection for the current study. Progressive multifocal leukoencephalopathy (PML) is a brain infection caused by the John Cunningham virus (JCV) and has been associated with natalizumab treatment, and to a much lesser degree with the oral treatments fingolimod and dimethyl fumarate (Broadley et al., 2015; Clifford & Nath, 2010). The PML infection has been reported in over 750 cases of RRMS with a greater than 20% fatality rate and a substantial morbidity in survivors (Biogen, 2018). PML is difficult to differentiate in PwRRMS because the symptoms of the brain infection can mimic MS symptoms and can be missed. There are algorithms to help MS HCPs and PwRRMS determine specific risks dependant on individual levels of JCV antibodies (measured on a blood test), on the number of infusions administered and on previously prescribed MS treatments. Other serious DMT side effects are related to treatment with alemtuzumab, and include serious autoimmune thyroid issues, idiopathic thrombocytapaenia purpura (a blood clotting disorder) and autoimmune renal disease (Coles et al., 2012). Ocrelizumab was not approved for use in Australia at time of data collection and did not feature in discussion in the participant interviews.

The current treatment landscape in Australia has a myriad of first line treatment choices for people diagnosed with RRMS, all with varying degrees of efficacy, risks and side effect profiles. Coupled with a rapidly expanding digital world with growing information of unknown quality and accuracy, it is no wonder that people diagnosed with MS face considerable stress coping with not just the disease and the decision making processes that go along with DMT treatment options, but also the uncertainty and unpredictability which are features of the disease. The lack of an accurate prognostication tool at the beginning of the disease trajectory can be both

frightening and frustrating for people diagnosed with MS and make it difficult to reach a comfortable decision on DMT choice (together with their MS HCP).

Controversial therapies

Even though there are many rigorously clinically proven DMTs to treat RRMS, patients can be so desperate for a cure that they will overlook the lack of carefully tested scientific evidence and consider unproven and potentially dangerous treatments (Bowman, Racke, Kissel, & Imitola, 2015). This is understandable as vulnerable patients search for answers to their illness, not just in the absence of a cure, but also in the setting of very serious effects from DMTs and the risk of disease progression, even when compliant with DMT.

One form of treatment which has been controversial in the past, but with continued research is becoming more accepted as a potential treatment in RRMS, is haematopoietic stem cell transplant (HSCT). This emerging therapy is being used for aggressive RRMS unresponsive to current DMTs, and is currently the subject of several international clinical trials (Dorr, 2016). Early results show great promise in improving neurological function and preventing new MS lesions (Atkins et al., 2016), however there is also a 5% mortality reported with the procedure and a general consensus on protocols and safety have not yet been established (Dorr, 2016). The evidence for using HSCT in certain individuals with RRMS is increasing and may be an effective treatment for specific situations, in the setting of careful patient selection and experienced staff (Alexander et al., 2018). However, outside of the clinical trials, some PwRRMS have resorted to "stem cell tourism" which a rising internet based industry that offers unproven procedures to people with incurable diseases, and in most cases involving travel overseas (Bowman et al., 2015). Once again, an understandable option to consider for people living with an unpredictable disease and uncertain future. It has been suggested that instead of seeing people who pursue unproven therapies as "desperate individuals duped by medical racketeers", they could be seen as "empowered citizens who have taken an informed decision to pursue an experimental therapy" (Mazanderani, Kelly, & Ducey, 2018, p.232).

A controversial treatment that has been shown to be ineffective in MS, but is still sought out occasionally by PwMS, is liberation therapy. This type of angioplasty was

postulated to correct a possible cause of MS, chronic cerebrospinal venous insufficiency (CCSVI), but has been proven to be ineffective (Zivadinov & Weinstock-Guttman, 2018). Combating the spread of viral internet popularity for this therapy proved difficult, as the value of the MS neurologist and HCP expertise was largely ignored in favour of emotionally resonant blogs, despite reported mortality of the procedure (Green, Kamel, & Josephson, 2018). In a recent study of 168 participants all living with RRMS, Chacinska et al. (2017) found that in their search for a cure, PwRRMS were likely to accept very risky treatments, with 81% of participants accepting a 1:100 mortality for the *chance* of a cure.

New therapies

Besides HSCT clinical studies described above, there are many new therapies for MS currently in development, with over 20 phase two and three studies in progress (Shirani, Okuda, & Stüve, 2016). Several of the new biological molecules, such as amiselimod, have shown promise in efficacy with improved side effect profiles over the current DMTs (Kappos et al., 2016), leading to a great deal of hope about future treatments and their positive and safer impact on not just RRMS, but all forms of MS.

Neurorehabilitation

An important adjunct to DMTs, especially after a relapse, is neurorehabilitation and physical therapy (Davies et al., 2016). Various forms of exercise such as weight training, Pilates and yoga have also been found to be useful in alleviating symptoms of MS and in building strength (Feinstein, Freeman, & Lo; 2015). Rehabilitation in both physical and cognitive forms is a key treatment for all phenotypes of MS (Haselkorn et al., 2015; Khan et al., 2016; Mitolo, Venneri, Wilkinson, & Sharrack, 2015).

MS and Pregnancy

As RRMS predominately affects women, is on the rise in young women and has a mean onset of 30 years of age, many affected by RRMS will be in the childbearing

years of their lives (Coyle, 2016; Miller, 2016). Pregnancy does offer some protection against relapses (most effectively in the final trimester) although there is a return to baseline risk as soon as the baby is born (Miller, 2016). There has also been the suggestion that there are long-term benefits from pregnancy on progression of the disease (Masera et al., 2015; Ponsonby et al., 2012) and that there are no negative effects from pregnancy on MS prognosis (Coyle, 2016).

Many DMTs are not approved for pregnancy and need to be ceased prior to conception, which is often difficult to manage in a person with active disease who wishes to conceive and become pregnant (Coyle, 2016). Women with RRMS also often face decisional conflict regarding motherhood, although pregnancy has been found to be safe for mother and baby (Prunty, Sharpe, Butow, & Fulcher, 2008).

Contemporary Issues in MS

Although many people with RRMS continue to work and be independent, there are impacts on self esteem, relationships and friendships, community involvement and social activities that can be all-encompassing (Holland & Madonna, 2005). PwMS often have concerns that their disease will have negative economic and psychosocial effects for them and their family, impacts on childbearing and parenting and also burdening their partner with the disease (Alwan et al., 2013). There have been reports of an increased rate of broken relationships in PwMS particularly with the onset of other co-morbidities after the diagnosis of MS, suggested as relating to increased stress and demands placed on the relationship (Thormann et al., 2017). Perceptions by the PwMS and their partner of being "less able" can also lead to feelings of loss within a marriage and increased frustrations in maintaining relationships (Tabuleau-Harrison, Haslan, & Mewse, 2016).

There has been a focus on lifestyle matters for PwMS in the last few years, as awareness of the impact of positive lifestyle choices on MS has heightened. These include adopting a holistic approach to the management of MS and to the positive effects of exercise, smoking cessation, reduction of alcohol consumption, activities that improve cognitive reserve and a healthy diet (Giovannoni et al., 2016).

Support and resources for people living with MS in Australia

The number of MS groups and organisations worldwide has increased over recent years as demand for services and support has increased along with patient numbers diagnosed with MS (Browne et al., 2014). Support services are perhaps more important now than ever, as treatments evolve and patient management becomes more complex. In Australia, the growth of public and private based MS clinics over the last decade have increased dramatically to meet the needs of patients, to enable timely and efficacious treatments and to monitor disease activity and patient safety as the new DMTs become part of the complicated treatment paradigm.

It has been reported that coordinated, multidisciplinary care is of greater benefit than medical care alone in MS (Thompson, 2011). The goal of MS clinics is to offer specialized, targeted multidisciplinary care. Recently, patient engagement in their own healthcare has been described as "the blockbuster drug of the century" and vital for improving outcomes in people with MS (Rieckmann et al., 2015). Achieving patient engagement happens in the setting of education, confidence building, encouraging treatment adherence, valuing the importance of quality of life, empowering through responsibility and providing credible sources of information (Rieckmann et al., 2015) These are all important functions of MS clinics and MS organizations in Australia, involving an expansive and multidisciplinary approach. The importance of continuity of care and in particular communication between hospital and community, has never been more important and MS Neurologists, MS Nurses and MS organizations are integral in this regard.

MS Australia (MSA) is the national peak body for people living with MS in Australia; active in research, advocacy, disease awareness, communications, information and support for people affected by MS, their families and carers (MSA, 2018). Working alongside MSA is Multiple Sclerosis Research Australia (MSRA), dedicated to funding, co-ordinating and accelerating MS research, with the aim of ultimately finding a cure for MS (MSRA, 2018). Both organisations are integral for patients and MS HCPs alike, by providing considerable support, advocacy and information resources.

Modern communication technology and MS

Since the advent of the electronic and digital age, information and support is much more easily and freely available for people living with MS. The way people retrieve health information has changed due to an abundance of new media technologies and a remarkable growth in health information being available online (Haase, Schultheiss, Kempcke, Thomas, & Ziemssen, 2012). Websites from all of the major country MS societies and research groups are frequently accessed across the globe for information on all aspects of MS. Blogs and online support groups are also popular with patients and their families and also provide a means of communicating for people who may otherwise be isolated.

However, there are also negative aspects associated with these forms of electronic communication, including information overload, accessing inaccurate and outdated information, and misrepresentation of information. The rapidly growing production of healthcare information increasingly leads to a situation of information overload for all people involved in healthcare, patients, doctors and nurses (Klerings, Weinhandl, & Thaler, 2015). Having web-based information is an important and rich resource in healthcare to support practice and learning, but can also create conflicting evidence and security in the information (Bullock, 2014). The issues of technology and the digital age bring their known set of issues to living with MS and may impact greatly on patient care, in both a positive and a negative way.

The role of the MS Nurse

MS nursing has developed as a specialty after first being introduced in the United Kingdom on the early 1990's (Quinn, Leary, & Bowen, 2014). Evolution of the role has intensified over the last decade as new and more complicated therapies have been developed, greatly expanding the skillset and knowledge base of the MS Nurse as a specialist (Burke, Dishon, McEwan, & Smrtka, 2011). Most developed countries recognise this unique specialty, although some countries report no nurses with this specific expertise (Browne et al., 2014). Australia has a strong MS Nurse educational and resource organisation supporting MS Nurses in their practice, Multiple Sclerosis

Nurses Australasia (MSNA), which is a member of the International Organisation of MS Nurses (IOMSN).

The MS Nurse plays a critical role in assisting patients at the time of MS diagnosis and understanding options for disease treatment and management (Ross & Thrower, 2010). MS Nurses also play a central role in assisting patients with finding outside support to assist them in coping with their MS and in recognizing conversion to MS from CIS at an earlier stage (Kennedy, 2013). Additionally, fostering hope to combat feelings of hopelessness in MS is pivotal to the nursing role (Morgante, 2000).

In a survey of patients with MS, it was commonly felt that they had received insufficient support and education from healthcare providers in understanding and dealing with their diagnosis (Solari et al., 2007). Many people will have difficulty coming to terms with the diagnosis of MS and will worry about the possibility of becoming disabled and the future impact on employment, income, relationships, and activities of daily living (Ross & Thrower, 2010). Nurses, as integral members of the multidisciplinary healthcare team, play a major role in the education and support of the patient, and often at crucial times in living with MS.

Situating the current study in MS care

This overview of MS in general and the intricacies and complexities of RRMS in particular that have been presented in this chapter, have demonstrated that RRMS is a difficult and uncertain disease to live with. There are so many facets to MS care, so many possible symptomologies and so much unpredictability. Negotiating "normal" life alongside RRMS brings many challenges that need to be understood by MS Nurses and other HCPs in order to provide optimal clinical care to each individual. The following chapter will orientate previous research and knowledge of the lived experience of RRMS to the current research study in the form of a literature review. The significant gaps in the literature will also be discussed and the strengths of the current study in addressing these gaps will be presented.