

Pain in MS Workshop – Scientific Report

Workshop Summary

MS Research Australia hosted a workshop on Pain in MS on 3rd October 2019 in Melbourne. This workshop was organised in response to a need identified by the 2016 MS Research Australia Research Priorities survey that research into pain was an area of importance to the MS community.

The workshop brought together allied health professionals, people living with MS, MS organisations, Pain Australia and Chronic Pain Australia, and researchers from other disease fields with an interest in pain, to discuss what is known about pain in MS as well as knowledge gaps, and how this can be overcome to improve overall quality of life.

The workshop opened with three people with MS and their personal journeys with pain, which were vastly different. Mr Stephen Papadopoulos, Dr Mary Webb and Associate Professor Desmond Graham talked in detail about their experiences with pain, the hurdles that they have encountered, and how they have tried to overcome these. They also shared their thoughts on what the MS community are looking for in the way of guidance and support to help with their experiences of pain.

The first scientific session provided an introduction and overview into pain in MS. Chairing the session was Dr Kristin Lefever, a neurologist from Mater Centre for Neurosciences QLD currently undertaking a PhD in pain in MS, who also spoke about the current literature on pain in MS. Mr Tim O'Maley, a MS nurse from the MS Queensland, spoke about the different types of pain and pain management, highlighting that there is no one size fits all approach. The session concluded with Associate Professor Ingrid van der Mei from the Menzies Institute for Medical Research TAS presenting the MS Research Australia-supported Australian MS Longitudinal Study and how it can be a new resource for research into pain.

The second scientific session covered pharmacological interventions for pain. Chairing the session was Mr Tim O'Maley who spoke about the different types of evidence based pharmacological treatments available for pain management and his experience with people with MS. Dr Leon Warne, a lecturer from Murdoch University and Head of Research and Innovation at Little Green Pharma WA, presented his work on gene therapy to reverse chronic pain as well as his research into medicinal cannabis for managing pain and improving quality of life. Dr Sam Duffy, a researcher from Griffith University, discussed his PhD on neuropathic pain in *in vivo* models of MS, which provided an avenue to test novel pharmacological compounds to treat pain in MS in the laboratory environment.

The third scientific session covered non-pharmacological interventions for pain. Chairing the session was Dr Jamie Young, a clinical pain specialist from the Peter McCallum Cancer Centre VIC with a PhD in pain in MS, who also provided an overview of non-pharmacological treatment options for pain management and an update on his research on MS-related pain. Ms Amy-Lee Sesel, a psychologist undertaking a PhD in MS at the University of Sydney NSW and funded by MS Research Australia, spoke about the preliminary findings of her mindfulness clinical trial as a pain management option for people with MS. Dr Litza Kiroopoulos a Senior Lecturer from the University of Melbourne and Adjunct Senior Research Fellow from Monash University, presented her research on cognitive behavioural therapy for the treatment of depression, anxiety, fatigue, poor sleep quality and pain.

The final session focused on bringing everything together and looking at the bigger picture to reduce pain and improve the quality of life for people with MS. Chaired by MS Research Australia's Deputy Head of Research, Dr Hamish Campbell, the session featured a presentation from MS Australia on raising awareness of the resources and platforms that already exist for pain in MS as well as advocacy in this area. There were also talks from Associate Professor Malcolm Hogg from Pain Australia who spoke about a national pain strategy and Ms Fiona Hodson from Chronic Pain Australia who spoke about general issues and considerations of chronic pain.

In depth discussion opportunities followed each session, allowing all delegates to contribute their perspectives, thoughts and expertise on this topic. Themes of the discussion included ways to close the communication gap between healthcare professionals and people with MS about their pain, the need for a multidisciplinary approach for clinical practice that includes both pharmacological and non-pharmacological interventions to help manage and treat pain. There was also discussion about the strength of current evidence into the safety and effectiveness of medicinal cannabis in managing pain, including the best way to fill the gaps in this area of research. A final discussion session aimed to draw together all the threads and themes that had been explored during the day, to arrive at some clear next steps to move the field forward.

The first clear outcome from this workshop was the need for more funding towards research into MS-related pain, which would pave the way to addressing the gaps in this area. This would provide much needed clarity around the topics discussed and ultimately improve the quality of life of people with MS who are experiencing pain. There was also discussion of organisations including MS Research Australia, MS Australia, Pain Australia and Chronic Pain Australia continuing to work collaboratively to raise awareness among the medical community regarding pain in MS and to bridge the communication gap between people with MS and clinicians. It is hoped that together these will help fill the gaps in pain MS and will ultimately improve the quality of life for people with MS who experience pain.

Workshop Proceedings

Background and Aims

One of the key priorities identified by people with MS in the MS Research Australia Research Priorities Survey was pain management. To address this prior MS Research Australia assembled, representatives from the MS community, neurologists, pain specialists, MS and pain researchers, allied health professionals and MS service providers to identify gaps and priorities in pain research.

This workshop was held on 3rd October 2019 in Melbourne and was the culmination of extensive discussions that took place between representatives from MS Australia, the State MS Societies and MS Research Australia at the April 2019 National Services Leadership Group (NSLG) meeting. It was agreed that pain was an important and unaddressed priority for people with MS, and within the Australian landscape, it was not an area that had received significant attention.

The development of this workshop was led by a steering committee of clinicians and MS professionals with experience in the issues involved with pain and MS: Dr Mary Webb (person with MS experiencing pain and MS Australia Advocate), Mr Tim O'Maley (MS Nurse from MS Queensland), Ms Sandra Walker (General Manager, Service Innovation, MS Limited – NSW, VIC, TAS, ACT), Mr Andrew Giles (National

Policy officer at MSA), Dr Julia Morahan (Head of Research, MS Research Australia) and Ms Arjanna Chitranjan (Research Translation Coordinator, MS Research Australia).

There were 29 delegates in attendance at the workshop including neurologists, pain specialists, MS and pain researchers, allied health professionals, MS service providers, six people with MS who experience pain and a family member/caregiver.

The workshop had the following aims:

- Based on what is known regarding pain in MS and challenges faced in its management and care, determine specific knowledge gaps that need to be addressed.
- Identify research areas and appropriate research designs to fill the knowledge gaps.
- Determine opportunities for collaboration and translation to improve pain related outcomes for people with MS.

Introduction

Perspectives of people living with MS related pain

Chair: Dr Julia Morahan, MS Research Australia

Mr Stephen Papadopoulos Fundraising Relationship Ambassador, MS

Mr Papadopoulos shared his personal experience of pain, which has been one of his main MS symptoms since his diagnosis 19 years ago. Mr Papadopoulos described his pain as severe.

In addition to his self-developed coping strategies such as the constant movement of legs and arms, very quick showers, and wearing long sleeves to avoid impact of the elements and human touch on his skin, Mr Papadopoulos has worked closely with his neurologist to manage his pain through pharmacological means. He reported having tried most pharmaceutical interventions (anti-depressants, anti-convulsive medications, etc.) currently available to people with MS to treat pain, with low to moderate success, with the exception of morphine patches. Mr Papadopoulos also discussed the side effects of pain medications and the importance of weighing these with the potential benefit.

Mr Papadopoulos has found cannabis products to be effective for managing his pain. He believes cannabis products have dramatically changed his experience of pain and improved his overall quality of life, and described reduced pain intensity, increased relaxation and an ability to obtain a better nights' sleep than his usual four hours per night. He further commented on issues with cannabis that he has, including a lack of clarity around access, optimal mode and dose of consumption, and undesirable side effects such as cognitive impairment.

Dr Mary Webb Freelance Editor and National Advocate, MS Australia

Dr Webb shared her experience of pain due to MS, and the continuously changing nature of her pain throughout her 20 years of living with the disease. She discussed the “invisible” and subjective nature of pain, and her difficulty in explaining her experience. She felt these reasons were why her pain has not always been taken seriously by medical professionals.

Dr Webb's self-developed coping strategies have included a change in career to avoid being on her feet, avoiding activities in the heat (which she has found exacerbates her pain), and wearing a tight sleeve on her arm to minimise friction.

Dr Webb has tried various pharmaceutical interventions, has found an anti-depressant prescribed by her neurologist to be the most effective as a long term strategy. She felt that her cognition may have been moderately affected as a side effect of this drug, which was being investigated further by her medical team.

Dr Webb also shared the non-pharmaceutical pain management strategies she has tried over the years such as acupuncture and psychological approaches prescribed by books and workshops she has attended, though these have not proven to be significantly effective in the management of her pain. However, Dr Webb relayed that a [recently published strategy](#) from MS Research Australia supported researcher A/Prof Ollie Jay to help people with MS combat heat by cooling their core temperature has helped her to manage her pain, which is exacerbated by the summer heat.

In conclusion, she expressed concerns regarding the severity of her pain increasing in the future, and being faced with having to move on to some of the "heavier" pain medications with undesirable side effects and impacts on her quality of life

**Associate Professor Desmond Graham
President, MS Australia Board**

Associate Professor Graham shared his journey with MS-related pain, including the significant changes he had to make to his lifestyle and career to deal with this symptom. He described his pain as a "mixed bag", and said that his focus along his pain journey has been on uncovering the triggers for his pain instead of focusing on the suppression of his pain.

Along his pain management journey, he has worked with multiple specialists and neurologists. More recently, he has worked towards minimising the use of his regular pain medication, oxycodone, which he found worked very well for the type of pain he was experiencing long term, but elicited undesirable side effects. A strategy that helped him "reset his pain receptors and withdraw from his medications in a supervised environment", was receiving ketamine infusions under a specialist anaesthetist.

Associate Professor Graham also emphasised the importance of an integrated approach towards managing pain in MS, which includes reaching out to others and accepting support, following a healthy diet, reducing obesity and adequate exercise.

Discussion

- There was a general consensus that pain in MS is heterogeneous and can change in intensity, location and sensation for the same individual over the course of their MS journey.
- Types of pain experienced by the attendees with MS were discussed, such as dull, stabbing, throbbing and burning.
- Other experiences included:

- An intense pain that felt like “a sharp knife wedged in the back of the neck and being twisted”.
 - An intense burning pain felt throughout the body, which caused increased sensitivity to friction from clothing, sunshine, touch, and even air.
 - Lhermitte's sign, a sudden, brief and painful sensation that feels like electricity passing through the body which usually occurs in response to bending the chin to chest.
 - Trigeminal neuralgia, a specific type of face pain.
 - A pain which starts in one location and spreads throughout the body like a vibration.
 - Bowel and bladder pain possibly arising due to the strain from lost muscle tone seen in people with MS.
- The main locations reported as being affected were the legs, head, back of neck, and along the spine.
 - All those present with MS agreed that there are a number of factors which make their experience of MS-related pain worse, with stress being one of key importance. Fatigue, sleep quality, and their confounding relationships with pain was also discussed.
 - Social isolation from having to give up hobbies and careers was highlighted as an outcome that significantly reduced the quality of life of people with MS living with pain.

Session 1 - Introductory overview

Mr Tim O'Maley

MS nurse Practitioner and Special Education and Community Resources Manager, MS QLD

Introduction to Pain in MS

Pain is the most common reason people seek medical help, with one in five GP consultations involving a patient with chronic pain. However, it is one of the most neglected and misunderstood areas of healthcare. It is reported that one in five Australians live with chronic pain, with its prevalence increasing to one in three people over the age of 65 (1).

The four main types of pain experienced by People with MS include:

1. Neuropathic nociceptive/deafferentation pain which occurs in the absence of a stimulus and produces sensations of electric shock, burning, shooting and stabbing.
2. Somatic nociceptive pain occurs due to ongoing noxious stimulation originating from bone, the fascia joints, tendons, ligaments and muscles. This results in a localised and aching pain.
3. Visceral nociceptive pain occurs through the stimulation of the nociceptors in areas such as the heart, lungs, bowel or bladder. This pain is dull, diffuse and poorly localised.
4. Pyschogenic syndrome occurs through cognitive and psychiatric disturbances and includes fear, worry, anxiety and depression.

The pain experienced by people with MS often varies in type, intensity and location. Individuals have different responses to treatment strategies, therefore there is no “one size fits all” management strategy for pain in MS. In developing pain management plans, side effects of various medications and symptoms an individual may be experiencing (such as fatigue, and issues with sleep, cognition, and mood) must be considered.

Rather than assessing individual episodes of pain, where appropriate it may be beneficial to consider the often chronic nature of pain and plan accordingly. There is a need for more “outside the box” thinking within the medical community regarding pain management in people with MS, including the diagnosis of pain (i.e. the cause of pain in people with MS can sometimes be unrelated to their MS or be side effects from their MS medication). Examples of misdiagnosed pain in MS include conditions such as bulging discs which are unrelated to MS, and complications from immunosuppressive effects of MS medication such as shingles.

Health literacy within the MS community is an important area that requires more advocacy and education in order improve. This will help address one of the major barriers reported in the management MS related pain in the clinical environment – clear communication between medical professionals and people with MS regarding pain.

Dr Kristen Lefever

Neurologist, Mater Health Services and Neuroimmunology Fellow, Queensland Health

Research into pain in MS and research gaps

Reports indicate between 20-60% of people with MS experience pain, with this number increasing to 70% of people with progressive MS (2). The discrepancy may be due to the variations in study design and people with MS downplaying their experience of pain. There is a need for high quality research studies in this area.

The most commonly reported types of pain by people with MS are neuropathic, nociceptive and mixed pain. Neuropathic pain includes headaches at 51%, neuropathic extremity pain at 26.6%, back pain at 20%, Lhermitte’s sign (a pain that runs down the neck and spine and radiates out the limbs) at 17% and trigeminal neuralgia (a specific type of pain in the face) at 4% (3,4).

Based on current evidence, it is clear that there are many cases where pain is present at diagnosis of MS, however it is not clear if it can be a marker of disease (3-8), highlighting the need for further research.

People with MS who report pain have higher healthcare needs and therefore, represent a higher economic burden, which increases as pain intensity increases (3). The impact of pain on the quality of life of people with MS is significant, as observed in a 10 year longitudinal study (4). Psychosocial factors also play a role in the experience and perception of pain (5).

Dr Lefever identified several areas that need further research, including

- Improvements in pharmacological and non-pharmacological interventions for the treatment of pain in MS
- Improved the assessment and monitoring of pain in MS, including standardisation of measurements and methods

- Better understanding of the biopsychosocial impact of pain overall.

General pain resources could also be used for the management of MS-related pain. Dr Lefever highlighted the Initiative on Methods, Management, and Pain Assessment in Clinical Trials (IMMPACT), which has made significant contributions towards the improved understanding of pain and its treatment. It operates to develop consensus reviews and recommendations for improving the design, execution and interpretation of clinical trials in the treatment of pain.

Associate Professor Ingrid van der Mei

ARC Principal Research Fellow, Menzies Institute for Medical Research and lead investigator of the MS Research Australia platform the Australian MS Longitudinal Study (AMSLS).

AMSLS overview and pathways towards pain research

The MS Research Australia platform, the [Australian MS Longitudinal Study \(AMSLS\)](#) is a patient reported outcome study and the cohort of this study has been independently validated and shown to be representative of the Australian MS population (6).

Pain data collected through the AMSLS confirmed what is already known in the literature about the incidence and prevalence of pain in people with MS and uncovered some novel trends:

- In this dataset, it was found that 40% of people with MS live with moderate to severe levels of pain, consistent with the range reported in the literature to-date (20-60%).
- Over a period of four years, the intensity of pain experienced by each individual in this study did not change greatly. This means that while people’s pain did not worsen greatly, there wasn’t any improvement either.
- When the relationship between pain and other MS symptoms was studied, a close correlation between sensory symptoms and pain was observed, which needs to be investigated further.
- Pain was shown to be one of the top two symptoms that impacts on quality of life of people with MS.
- Pain was also associated with significant work productivity loss in people with MS.
- People with MS with a higher disability or a higher self-reported progression experienced more pain.
- Age, gender, disease duration, MS type or onset type were not significantly associated with the level of pain experienced by people with MS.
- Over 85% of people have comorbidities and these contribute towards the increased pain severity of a person with MS, with musculoskeletal and mental health conditions contributing most.

Discussion (Chair - Dr Kristen Lefever)

- The underappreciation of pain in MS by medical professionals was discussed by the people with MS. The importance of raising awareness among the medical community about pain in MS and improving health literacy among the MS community to bridge the communication gap between people with MS and medical teams regarding pain was highlighted.

- It was pointed to that while evidence suggests GPs and neurologists are commonly consulted by people regarding their pain, dissatisfaction levels associated with the resulting pain management were high. Some of the reasons for this dissatisfaction were the superficial assessment of pain by clinicians due a lack of time, failure to appreciate the need for multidisciplinary pain management strategies, and the long waiting lists for pain specialist referrals.
- The low levels of collaboration and communication between MS specialist/neurologist clinics, tertiary pain clinics and integrative rehabilitation clinics was identified as a critical issue that impedes multidisciplinary management of MS-related pain.
- The possibility of leveraging tools that are already in use within the clinical environment such as the chronic pain platform [ePPOC \(electronic persistent pain outcomes collaboration\)](#) to record and monitor long term pain related outcomes for people with MS, and resources available for clinicians and those experiencing pain on the [Pain management network platform](#), was discussed.
- There is a need to expand the ePPOC to include more pain management clinics nationally, and to adapt the criteria to identify MS as a condition on its own, rather than within the “other/neurological conditions” category. This would facilitate the extraction of MS-specific data. Of the 49,037 people captured by the database, 148 are recorded as having MS. This is likely to be a significant underestimation due to the lack of an independent category.
- Issues around the practicality of integrating the use of pain-related tools within the relatively short amount of time available during medical consultations were discussed.
- The need for robustly designed, patient-centred studies was discussed as being required for improve our understanding on the experience of pain in people with MS and their journey with pain management.
- The delegates discussed the possibility of developing a MS-specific pain scale for research purposes, versus the use of an existing, more generic pain scale. While it was noted that a MS-specific scale might be useful, the use of a generalisable scale was looked upon more favourably as it allows comparisons between different conditions.
- The importance of ensuring that quality of life measures are included is a key outcome in MS-related pain research was highlighted.
- The delegates discussed the need for guidelines for neurologists and people with MS on the assessment and management of pain, with the hope that this would be a solution to the existing communication barriers between healthcare professionals and people with MS experiencing pain.

Priorities for translation

- There remains a gap in the understanding of the epidemiology of pain in MS, which will require adequately powered and well-designed cohort studies, and ideally longitudinal pain data from the time of MS diagnosis.

- There needs to be increased research into types of pain that are prevalent in people with MS (most research concentrates on trigeminal neuralgia), to gain a more accurate picture of pain experienced by people with MS.
- There is also scope for more complex research that investigates the relationship between pain and relapses, lesion location, disease modifying therapies, specific MS symptoms and comorbidities in MS.
- There is a need for an adequate measurements responses to pain strategies in practice and under investigation, which translate to actual improvements to the quality of lives of people with MS, beyond data that is only statistically significant. Therefore, more research is needed to integrate existing pain rating scales and quality of life measures, to develop a practical and relevant tool.
- Communication tools that bridge the gap between clinicians and people with MS experiencing pain are needed to ensure that the pain experience is captured and the management of pain is appropriate and successful.

Practicalities of translation

- Researchers and clinicians cautioned that low enrolment numbers, limited adherence and high attrition rates have been long-standing issues in clinical pain research.
- The underestimation of pain due to the common underreporting of pain by those experiencing it will pose challenges.
- The limited capacity within a busy clinical environment to appropriately assess pain, and therefore contribute towards ongoing research and integrate the latest research findings into clinical practice will be challenges to overcome. A possible solution will be providing education on pain to undergraduate medical students, GPs and staff in tertiary pain centres, especially since pain specialists have long waiting lists. This will allow people with MS who experience pain to be assessed regularly.

Session 2 - Pharmacological interventions for pain in MS

Mr Tim O'Maley

MS nurse Practitioner and Special Education and Community Resources Manager, MS QLD

Clinical treatment of pain

A range of medications are currently available in Australia for the treatment of pain. Pregabalin and amitriptyline hydrochloride are the most commonly prescribed pain medications for people with MS, and these medications account for 85% of total prescriptions at the MS Queensland clinic. Currently available options include:

Drugs for neuropathic pain:

- Drugs that stabilise the cell membrane: anti-epileptics (phenytoin, clonazepam etc. which are older and have undesirable side effects such as sedation and weight gain, and newer agents which are better tolerated such as gabapentin and pregabalin) and corticosteroids.

- Drugs that alter signalling processes along the spine by inhibiting the dorsal horn: antidepressants (amitriptyline, imipramine or newer agents such as duloxetine and venlafaxine, which have undesirable side effects like dizziness, nausea and weight gain) and anti-epileptics.
- Anaesthetics such as ketamine, and opioids such as methadone which have undesirable side effects such as drowsiness and constipation.

Drugs for nociceptive pain:

- Drugs that work by inhibiting the production of prostaglandin: salicylate (Aspirin), paracetamol and non-steroidal anti-inflammatory drugs (NSAIDS) such as ibuprofen. These medications can have side effects such as fluid retention, constipation and peptic ulcers.
- Cannabis and weak opioids: cannabis products (Sativex mouth spray and many other products which have some side effects such as dizziness and tiredness) and weak opioid receptor agonists (tramadol which has no withdrawal effect but have undesirable side effects such as sedation and dizziness).
- Opioid agonists: opioid products (morphine, codeine, methadone etc., which are addictive substances that cause side effects such as constipation, fatigue and cognition/mood changes) are used to treat pain in MS. Their methods of delivery can vary from oral to intrathecal pumps.

Efficacy of pain medications can vary considerably depending on the individual case and for some medications, a titration process is required to determine a suitable dose. This often requires collaboration between medical teams, and patient adherence. This process can sometimes take up to a year.

There are some points of concern regarding the use of pharmacological interventions to treat pain in MS:

- Lack of adherence to the pain medications being prescribed due to the taboo associated with their more common uses in conditions other than pain (such as depression, ADHD and epilepsy) and a lack of education or explanation of this from medical teams.
- The debilitating, commonly occurring side effects of pain medications such as fatigue and cognitive impairment.
- Pain medications may have detrimental interactions with other medications taken by people to treat their MS.
- Lack of understanding among patients who may expect a “one pill fixes all”, and that many drugs that are effective for the management of neuropathic pain (e.g. corticosteroids) are not suitable for long term use.

Multidisciplinary management of pain is key. In the MS Queensland clinic, more than 95% of people with MS report having tried complimentary/alternate pain management strategies at some point along their pain journey. A multimodal pain management strategy that involves exercise, relaxation/meditation, mental health and vocational support is important and will likely be the most effective.

Dr Leon Warne

Head of Research and Innovation, Little Green Pharma, veterinary anaesthesia and pain management lecturer, Murdoch University, and Head of MS Pain Research Group, Harry Perkins Institute

Emerging therapies for pain – clinical perspective and cannabinoids

Medicinal cannabis is currently approved for a range of indications by the TGA including neuropathic pain (more information here <https://www.tga.gov.au/access-medicinal-cannabis-products-1>).

While there are currently no specific indications or conditions predefined by the TGA that are approved for treatment using medicinal cannabis, a total of 55 different indications were approved to receive medicinal cannabis treatment in October 2018. Most medicinal cannabis applications approved by the TGA (>17,000 applications through the Special Access Scheme (SAS) or Authorised Prescriber Scheme) in Aug 2019 were for the treatment of pain associated with cancer symptoms the second most common was for the treatment of epilepsy which followed closely behind. There remains a promising window to explore its effectiveness in treating MS related pain and other symptoms. At present, the body of evidence available to-date regarding the effectiveness of medicinal cannabis to treat MS symptoms is inconclusive. Evidence to support its effectiveness in MS pain is low, and MS spasticity is moderate (7-11).

There are some common side effects experienced from medicinal cannabis use such as tiredness, dizziness, feelings of euphoria, nausea, changes in appetite, and increased heart rate, and this highlights that further investigations are needed in this area.

The medical industry is in a unique position with respect to medicinal cannabis versus other pharmacological interventions. This is largely due to the high consumer demand for a product that is yet to attain sufficient amounts of evidence supporting its efficacy, which has led to prescriber reluctance. This collectively results in a huge gap in supply and demand, which could be addressed with more research. There is a medicinal cannabis product with TGA approval, sativex, a cannabinoid based oral spray that is currently approved for spasticity in people with MS though this has not been approved for pain indications.

Dr Sam Duffy - Griffith University

Biological pathways and novel treatment angles

Dr Duffy carried out his PhD on neuropathic pain in *in vivo* models of MS. This model was established by Dr Duffy and his colleagues at the University of NSW, which provides an avenue to test novel pharmacological compounds to treat pain in MS in the laboratory environment.

This type of research is important to continue to uncover compounds that are novel and can address the unique nature of neuropathic pain by better understanding the biological pathways/biomarkers that might be unique for people with MS.

A type of immune cell, called T regulatory (Treg) cells, plays an important role in immune homeostasis, and ablation of these cells is necessary to generate *in vivo* models of MS. Delivering Treg cells and a molecule it secretes, called interleukin-35 (IL-35), into models of MS reduced pain behaviours independent of disease progression (12). Both stimulus-evoked pain and spontaneous pain were

reduced in models injected with Treg cells compared to those models injected with saline only as a control. Increased myelination in the brain after IL-35 treatment was also observed, suggesting a regenerative role on myelin most likely mediated by Treg cells.

Further work is now needed to better understand the Treg and IL-35 mediated reduction in pain, and translate this work to humans, to assess its effectiveness in people with MS experiencing pain.

Discussion (Chair - Mr Tim O'Maley)

- There is significant diversity in the pain experience of a single patient over time and across different patients. Coupled with the high variability of other MS symptoms and the potential for interaction, management must be tailored to each individual.
- Correct diagnosis of the type of pain a person is experiencing may increase access to the appropriate medication or management technique for pain and needs to be considered.
- It is important that side effects from prescribed pharmacological interventions are balanced with overall quality of life (QoL). Integrating self-reported QoL measures into the assessment of the efficacy of a management strategy may aid this.
- Difficulties regarding access of medicinal cannabis in Australia was discussed. There is a lack of knowledge within the medical community regarding Therapeutic Goods Administration (TGA) processes and limited awareness around referral pathways to obtain medicinal cannabis products that are manufactured in Australia. This may contribute to people obtaining medicinal cannabis outside of the current regulatory framework. Medicinal cannabis sold outside of the current regulatory framework may have unregulated pricing and quality.
- There were concerns raised about the TGA not collecting patient outcomes after treatment with medicinal cannabis, and several delegates were lobbying the government to capture this information.

Priorities for translation

- More research is needed to better understand the biological pathways associated with pain in MS, in order to develop novel pharmaceutical agents that help reduce MS related pain with minimal side effects.
- More research is needed on medicinal cannabis and its efficacy in pain in MS, in an effort to bridge the gap between the demand from people with MS who believe it to be effective in treating pain and the lack of supporting evidence for this in the current literature.
- More education tools must be developed to aid clinics that manage MS-related pain to improve communication with patients regarding pharmacological interventions being prescribed, including their side effects, this may alleviate the low adherence seen in some people with MS.

Practicalities for translation

- The interactions of pain with other existing MS symptoms, the interaction of pain medications with existing MS symptoms and the possible side effects that impact QoL must be considered when developing pharmacological interventions for people with MS experiencing pain both in the research and clinical environments.

- Patient reported outcomes relating to their pain and overall QoL must be objectively quantified and integrated into assessing the effectiveness of pharmacological treatment strategies to ensure research outcomes can be translated to patients.

Session 3 - Non Pharmacological Interventions in MS

Dr Jamie Young - Pain and Rehabilitation specialist, Peter MacCullum Cancer Centre

Overview of non-pharmacological options for pain management

Non-pharmacological interventions are defined as any intervention that does not involve pharmaceutical or surgical methods. There are a range of non-pharmacological interventions that are used to treat pain in MS and these options can be attractive as they can be integrated into management with pain medications and are suitable for long term use. Options include:

- Lifestyle changes (such as exercise, reduced alcohol consumption etc.)
- Psychological approaches (such as promotion of emotional wellbeing, mindfulness etc.)
- The reduction of psychiatric comorbidities and/or symptoms of MS such as anxiety and depression
- The improvement of coping strategies for those living with MS-related pain (including counselling, cognitive behavioural therapy, education)

A ten year observational study examined the long term effects of chronic pain on the lives of people living with MS in Australia (13). The study found that while 44% of people used non-opioid analgesics to manage their pain, 64% reported using non-pharmacological interventions such as massage, hydrotherapy and electrical stimulations.

Dr Young and colleagues conducted a Cochrane Review into whether non-pharmacological interventions are effective in reducing chronic pain in MS (14). Cochrane Reviews rigorously assess evidence from a range of studies to draw conclusions. The team concluded that there are significant benefits to the management of pain from the use of various non-pharmacological interventions such as transcutaneous electrical nerve stimulation (TENS), transcranial direct-current stimulation (tDCS), reflexology, hydrotherapy and psychotherapy were seen in clinical trial settings. Dr Young and other authors of this review concluded that further investigations in larger patient cohorts are needed to confirm the findings, and translate them to clinical practice.

The ePPOC registry is a platform that has the potential to facilitate much needed further research into the effectiveness of pain management strategies in MS, particularly non-pharmacological, on a national scale. While improvements are required to this platform for its use in people with MS, this registry has been used successfully to track pain in people with central neurological disorders, which includes people with MS. Using data from this registry, Dr Young identified that a decrease in pain, anxiety, stress, and an increase in self efficacy was observed in people with central neurological disorders, including MS, who took an interdisciplinary approach to their MS care.

Dr Young is carrying out further work on continuous electrical stimulation and its potential to treat pain, and has found that this treatment is effective in decreasing pain intensity in those experiencing

chronic neuropathic pain as a part of their MS for up to two weeks post-treatment, though no changes to their overall quality of life, depression or anxiety have been reported.

These findings highlight the importance of taking an interdisciplinary approach to addressing pain, with the integration of pharmacological and non-pharmacological interventions and the need for more robust research to delineate the most effective non-pharmacological strategies to improve pain related outcomes for people with MS.

Ms Amy-Lee Sesel

Clinical Psychology Registrar and PhD candidate, University of Sydney

Preliminary findings on the effect of mindfulness on MS pain

MS Research Australia funded researcher and clinical psychologist Ms Sesel is conducting a clinical trial that looks into a psychological intervention (mindfulness) program and its effects on outcomes such as QoL and pain in people with MS. This study aims to address the comorbidities that people with MS (who also experience pain) commonly report such as an increase in depressive symptoms (15), diminished physical functions (16) and the overall reduced mental and general health compared to people with MS who do not experience pain (17).

Ms Sesel's clinical trial has progressed well, with high adherence rates. Early analyses reveal that 60% of the people with MS who enrolled in her study experience pain, consistent with published literature. The mindfulness intervention did not significantly improve outcomes for people who only experienced pain. For those who experienced pain and depression there appeared to be improvement following the mindfulness intervention (unpublished data).

While further work will be required, mindfulness interventions may be particularly effective in the management of pain in people with MS who also experience depression, and it may be beneficial to integrate this into clinical care.

Dr Litza Kiropoulos

Senior Lecturer, University of Melbourne and Adjunct Senior Research Fellow, Monash University

Preliminary findings on the comparison of the ACTION-MS trial

MS Research Australia funded researcher Dr Kiropoulos is conducting a study using a cognitive behavioural therapy (CBT) intervention for the treatment of depression, anxiety, fatigue, poor sleep quality and pain. This study compares the effectiveness of a tailored cognitive behavioural therapy with a supportive listening intervention for depression and pain in those newly diagnosed with MS: the ACTION-MS trial.

Results from this study showed that there were significantly lower levels of pain along with the other comorbidities (anxiety, fatigue and poor sleep) reported by the patients who received CBT, accompanied by high levels of participant satisfaction.

Based on these results, Dr Kiropoulos has begun a second study, to assess the efficacy of a tailored CBT intervention in conjunction with supported listening for the treatment of depression, anxiety, fatigue and pain in MS.

This research highlights the importance of considering pain and its interaction with other commonly occurring comorbidities holistically within the clinical environment, to achieve the best possible outcomes for people with MS.

Discussion (Chair - Dr Jamie Young)

- The discussion echoed the closing comments of the presenters in this section – that more robust research is required to determine which non-pharmacological treatments are effective for long term management of pain in MS.
- The role of supplements as potential treatments for pain was discussed. While there is a perception that they may be beneficial for some people with MS, there is limited evidence supporting their use to improve pain outcomes for people with MS and no supplement is currently recommended in the pain treatment space.
- The discussion also highlighted the need for clinicians to assess the patient holistically and manage pain by combining pharmacological interventions and non-pharmacological interventions.

Priorities for translation

- More research is needed to identify the most effective non-pharmacological interventions to manage pain in MS through robust studies designed specifically for people with MS.
- Neurologists and GPs need more education regarding the non-pharmacological interventions that are ongoing/under investigation at other general pain centres and clinics, which may benefit people with MS.
- Interdisciplinary referral pathways that include non-pharmacological interventions must be identified and implemented in the MS clinics.

Practicalities of translation

- Low adherence rates among subpopulations of people with MS experiencing more severe pain which also often correlates with higher levels of disability, was anticipated to pose a barrier towards long term research in this area.
- Complexities were discussed regarding making pain records visible across clinics to facilitate clinical research and the multidisciplinary management of pain.

Session 4 – The bigger picture

A/Prof Malcolm Hogg

Board member, Pain Australia, Head of Pain Services, Royal Melbourne Hospital and Clinical Associate Professor, University of Melbourne

Australia's National Pain Strategy: from conception to implementation

- The significant impacts of pain on quality of life, participation in community, work and education, including its economic burden is well-studied, documented, understood, and acknowledged nationally (18).

- The majority (56%) of Australians living with chronic pain report that their pain restricts daily activities (18).
- On average, Australians with chronic pain are estimated to be absent from work for an additional 8.6 days per year compared to people without chronic pain (18).
- The total economic cost associated with chronic pain in Australia was estimated to be \$73.2 billion in 2018. This consists of \$12.2 billion in health system costs, \$48.3 billion in productivity losses and \$12.7 billion in other financial costs (informal care, aids and modifications, and deadweight losses) (18).
- People with chronic pain experience a substantial reduction in QoL, which has been valued at an additional \$66.1 billion (18).
- These costs equate to \$22,588 per person with chronic pain (18).
- The costs are expected to increase from \$139.3 billion in 2018 to \$215.6 billion by 2050 in 2018 dollars (in the absence of changes to treatment or prevalence rates) (18).

Pain in MS is predominantly chronic in nature, and there remain gaps in its assessment and management. Barriers to optimal assessment and management include cost, location, low awareness of treatment options or lack of access to appropriate healthcare professionals with knowledge and skills in pain management. Some of the consequences include psychological illness, social exclusion, financial disadvantage and possible over-reliance on pain medications such as opioids.

In order to improve outcomes for people living with pain, Australia's blueprint for the management of pain was developed in 2010. The key priorities of the [National Action Plan for Pain Management](#) are outlined below:

- **Recognise people in pain as a national public policy priority.**
- **Inform, support and empower consumers to understand and manage pain** through community awareness campaigns, consumer information resources and support.
- **Inform and support health professionals to deliver evidence-based care** by developing an overarching education strategy, expanded training opportunities and a validated assessment and monitoring tool for use across the board. The roll out of a Pain specialist designed and led national GP training program has been proposed (costing \$45m but saving \$209m).
- **Provide consumers with timely access to effective pain management** services by possibly utilising the Medicare system to improve access to pain management and doubling access to multidisciplinary care. The rough costs were estimated to be \$70m per year, saving \$271m through reduced health system costs and absenteeism.
- **Continuously evaluate and improve pain management across settings** through the implementation of a best practice pain management across all relevant services and care setting.
- **Implement a national research strategy to improve knowledge and translation** by the establishment of a new National Institute of Pain Research (NHMRC funded), following a similar trajectory as the recently established Research [Institute for Dementia](#), which exists as a virtual institute.

Ms Fiona Hodson

Board Member, Chronic Pain Australia and Office Bearer, Australian Pain Society

Chronic pain – general issues and considerations

Chronic Pain Australia conducted [a survey](#) of people living with chronic pain in 2019 as part of National Pain Week. The survey was completed by 1,252 people living with chronic pain, of which nearly 85% were female with an age distribution of 45-65 years. Findings are outlined below:

Pain management through GPs

- 41% of respondents reported seeing their GP at least monthly for their chronic pain, 19% fortnightly and 5% weekly.
- An average score of 8/10 was given for how those living with chronic pain felt their pain was being managed by their GPs.
- Respondents highlighted the importance of GPs listening to patients, the difficulties patients may have when explaining their pain and considering potential side effects of potential pain medications before prescribing.
- The number one thing those living with chronic pain wish their GP could do to help was prescribing medical marijuana/cannabis oil to treat their pain.

Pain management through pharmacists

- 37% of respondents reported seeing their pharmacist at least monthly for their chronic pain, 20% fortnightly and 11% weekly.
- An average score of 8/10 was provided for how those living with chronic pain felt their pain was being managed by their pharmacists.
- Respondents highlighted that they do not want to be treated as if they are addicted to their pain medication, that pain relief is a necessity not a choice and that pharmacists need to provide advice on better alternatives and new pain management options with thorough explanations.

Pain management through other health professionals

- 30% of respondents reported seeing pain specialists for their management. 40% saw physiotherapists and 15% psychologists to manage their pain. 10% did not seek help outside of their GP.
- 60% of the health professionals were accessed through GP referrals.
- Half of those living with chronic pain who filled out this survey found accessing these professionals easy, while the other half reported they found it difficult.
- Respondents felt that there was a greater level of understanding of pain and overall better management from using a multidisciplinary approach.
- Nearly 85% of those who saw health professionals find them unaffordable.

Government support

- Respondents identified the following ways government could support those experiencing pain:
 - full or partial rebate should be provided for the access to allied health professionals who manage chronic pain

- affordable treatments
- easier access to the National Disability Insurance Scheme (NDIS)
- medicinal cannabis being made available on the Pharmaceutical Benefit Scheme (PBS)
- better funding for pain exercise clinics

Stigma

- People living with chronic pain rated their feelings of being stigmatised or experiencing negative attitudes as significant at a 7 (where 1 was not at all and 10 was constant), including experiences with healthcare professionals.

Medicinal cannabis

- There were mixed thoughts by the people living with chronic pain who filled out this survey regarding the use of medicinal cannabis for pain management: some thought the use of medicinal cannabis to treat chronic pain is important and would like to try it, while others acknowledged more studies were needed in this area.
- About 64% of people living with chronic pain had not spoken with their GPs about accessing medicinal cannabis.
- Medicinal cannabis also suffers from issues of access, reluctance of GPs to prescribe and the high costs.
- The [Pain Management Network](#) is currently in place for people experiencing pain and provides information for the general public (general pain facts, lifestyle, nutrition and psychological health guidelines) and medical professionals (assessment, management, quick steps through opioid management and quick step guides to manage chronic pain in primary care). This resource may also be useful for people with MS and those treating them.

Mr Andrew Giles

National Policy Officer, MS Australia

Pain in MS – an advocacy response

Information presented on the day by Dr Hamish Campbell from MS Research Australia

Pain in MS potentially represents an opportunity for the type of systematic review that is conducted by MS Australia on behalf of the state MS organisations and people with MS. MS Australia is active in this area and there are a number of ways that this could be expanded:

- Continue to expand awareness amongst the broader (MS) community that pain can be an “[invisible symptom](#)” of MS.
- There is a [resource developed by MS Australia](#) that acknowledges pain as a key symptom of MS, a detailed [pain fact sheet](#) and tools which people with MS can prefill and bring along to their appointments with specialists to help begin the conversations regarding pain.
- There is scope to provide more information about pain in MS, and circulate existing and new evidence-based resources.
- Lobby the Australian Government to advocate for the needs of people with MS.

Discussion (Chair: Dr Hamish Campbell)

- There is a range of useful information and infrastructure that exists for pain in general, that could be adapted to improve outcomes for people with MS who experience pain.
- The availability of tertiary pain clinics varies depending on location within Australia (e.g. none at all in ACT), which greatly influences access to gold standard care. The lack of specialist pain clinics will also impact on research that requires clinics for recruitment and involvement in studies.
- The use of standardised pain forms can be a great asset for people with MS to maximise their time with their neurologist and bring attention to their pain management. One example is the pain form nominated in *the book Multiple Sclerosis Advances in Psychotherapy – Evidence-Based Practice* (19), which people with MS can complete prior to a consultation with a clinician.

Priorities for translation

- Raise awareness amongst clinicians and researchers within the MS pain space regarding the resources and platforms that already exist (some resources linked in below), to avoid duplication of work.
- Empower people with MS living with pain to advocate for themselves and contribute information to those that advocate for them by participating in surveys conducted through platforms such as the AMSLS.

Practicalities of translation

- Cross disciplinary collaboration on a large scale (possibly led by a national steering committee) is required to drive translation in this area that is meaningful, sustainable and well embedded within the clinical system.

Session 5 - Final outcomes

Chaired by Dr Julia Morahan

Opportunities for Research

- There is a gap between the experience of pain in MS and perception of pain in MS from others. Develop a consensus on ways to quantify the experience of pain in MS and treatment which would also be able to be used for research purposes and translates to actual improved outcomes in pain according to people with MS.
- Novel pharmacological therapies for pain management with less side effects are needed, that may benefit the proportion of people with MS that are not adequately able to manage their pain. Further research to identify new targets and therapeutics for pain is required.
- There is also a need to improve the evidence base for the use of medicinal cannabis for the treatment of pain in MS, determine whether the existing gap between patient demand and advice from the medical community can be narrowed or even closed.
- More robust research is needed into non-pharmacological interventions, to improve the quality of supporting evidence available, and to provide clarity around options that are most effective for people with MS experiencing pain.

- There is an opportunity to develop pain as a significant focus of patient reported outcome research, through longitudinal surveys (such as the AMSLS and other platforms) to gain a more accurate picture of pain affecting people with MS. This information can also be used to empower patients to proactively drive their own clinical care and improve outcomes.
- Resources that are currently available to capture pain outcomes, such as the ePPOC, need improvement to be useful for MS-specific pain research.
- More research could inform treatment choices for people with MS experiencing pain. At present, a range of pharmacological and non-pharmacological options are available and information is needed on how these combinations could be optimised for each individual circumstance.
- More research is needed on those that provide care for those living with MS-related pain, the results of which need to be factored in when making provisions for those living with pain through government benefit schemes.
- More research is needed to further delineate the relationship between work productivity and the economic impacts of MS-related pain.
- Funding for more research in this area through a targeted call for research in to pain in MS would enable momentum on the above objectives.

Opportunities for clinical improvements

- A multimodal approach must be employed to improve the management of pain, where pharmacological and non-pharmacological interventions are considered and prescribed as appropriate.
- A multidisciplinary/collaborative approach is needed within the clinical environment to manage and treat pain. This can be achieved by encouraging collaboration and cross communication between tertiary pain clinics and MS clinics.
- A national consensus should be reached for the management of pain in MS in Australia, and guidelines developed for best practice for clinical care of MS related pain.

Opportunities for advocacy and education resources

- Communication tools are needed to raise awareness among the medical community regarding pain in MS and to bridge the communication gap between people with MS and clinicians.
- Resources on pain are available. Education initiatives are needed to enable people living with MS, their medical teams and carers to raise awareness of their existence and to use and implement them in an effective way. One suggested initiative was the development of a pain education model in collaboration with MOOC (Massive Open Online Courses), developed by the University of Tasmania, which already hosts an award winning course [“Understanding Multiple Sclerosis”](#).

Useful Resources

[A proposed classification for Pain in MS](#) – a systematic review

[The Australian MS Longitudinal Study \(AMSLS\)](#) – potential for research collaborations, patient reported surveys on pain

[ePPOC \(electronic persistent pain outcomes collaboration\)](#) – potential for research collaborations, record and monitor long term pain related outcomes

[Pain Management Network](#) - information for the general public (general pain facts, lifestyle, nutrition and psychological health guidelines) and medical professionals (assessment, management, quick steps through opioid management and quick step guides to manage chronic pain in primary care).

[Pain form for completion prior to clinical appointments by people with MS](#)

[National Pain Week Survey, Chronic Pain Australia](#) – pain related information obtained from survey responses from people experiencing pain, GPs, pharmacists, other health professionals and federal government representatives.

[National Action Plan for Pain Management, Pain Australia](#) - Australia's blueprint for the management of pain, developed in 2010.

[TGA approval process](#) – information regarding the access of medicinal cannabis, and breakdown of approvals.

[Understanding pain in less than 5 minutes, Chronic Pain Australia](#) - video

[Invisible symptoms of MS, MS Australia](#) – video

[Pain in MS, MS Australia](#) - information sheet

[MS Pain Fact Sheet, MS Australia](#) – key facts and figures

References

1. **Pain Australia.** *Painful facts.* [Online] <https://www.painaustralia.org.au/about-pain/painful-facts>.
2. *Prevalence and natural history of pain in adults with multiple sclerosis: systematic review and meta-analysis.* **Foley, PL, et al.** 4, 2013, *Pain*, Vol. 154, pp. 632-642.
3. *Persistent pain and uncomfortable sensations in persons with multiple sclerosis.* **Hadjimichael, O, et al.** 1-3, s.l. : Wolters Kluwer, January 2007, Vol. 127, pp. 35-41.
4. *Chronic pain in multiple sclerosis: A 10-year longitudinal study.* **Young, J, et al.** s.l. : Elsevier, July 2017, *Scandinavian Journal of Pain*, Vol. 16, pp. 198-203.
5. *Psychosocial approaches to pain management: an organizational framework.* **Jensen, MP.** 4, Washington : Wolters Kluwer, April 2011, *Pain*, Vol. 152, pp. 717-725.
6. *Assessing possible selection bias in a national voluntary MS longitudinal study in Australia.* **Taylor, BV, et al.** 12, s.l. : Sage Journals, 2013, *Multiple Sclerosis*, Vol. 19, pp. 1627-1631.
7. *Cannabinoids for Treatment of MS Symptoms: State of the Evidence.* **Rice, J and Cameron, M.** 8, Oregon : SpringerLink, June 2018, *Current neurology and neuroscience reports*, Vol. 18, p. 50.
8. *Pain Modulation after Oromucosal Cannabinoid Spray (SATIVEX®) in Patients with Multiple Sclerosis: A Study with Quantitative Sensory Testing and Laser-Evoked Potentials.* **Turri, M, et al.** 3, s.l. : MDPI, 2018, *Medicines (Basel)*, Vol. 5.
9. *Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies.* **Stockings, E, et al.** 10, s.l. : Wolters Kluwer, October 2018, *Pain*, Vol. 159, pp. 1932-1954.
10. *The Use of Cannabis and Cannabinoids in Treating Symptoms of Multiple Sclerosis: a Systematic Review of Reviews.* **Nielsen, S, et al.** 2, s.l. : SpringerLink, February 2018, *Current neurology and neuroscience reports*, Vol. 18.
11. *Systematic review of safeness and therapeutic efficacy of cannabis in patients with multiple sclerosis, neuropathic pain, and in oncological patients treated with chemotherapy.* **Amato, L, et al.** 5-6, s.l. : E&P, 2017, *Epidemiologia e prevenzione*, Vol. 41, pp. 279-293.
12. *Regulatory T Cells and Their Derived Cytokine, Interleukin-35, Reduce Pain in Experimental Autoimmune Encephalomyelitis.* **Duffy, SS, et al.** 12, s.l. : PMC, 2019, *Journal of neuroscience*, Vol. 39, pp. 2326-2346.
13. *Chronic pain in multiple sclerosis: A 10-year longitudinal study.* **Young, J, et al.** July 2017, *Scandinavian journal of Pain*, pp. 198-203.
14. *Non-pharmacological interventions for chronic pain in multiple sclerosis.* **Amatya, B, Young, J and Khan, F.** s.l. : Cochrane Library, December 2018, *Cochrane database of systematic reviews*.
15. *The scope and nature of pain in persons with multiple sclerosis.* **Ehde, DM, et al.** 2006, *Multiple Sclerosis*, pp. 629-638.
16. *Chronic pain in a large community sample of persons with multiple sclerosis.* **Ehde, DM, et al.** s.l. : Sage journals, 2003, *Multiple Sclerosis*, pp. 605-611.

17. *Pain prevalence, severity and impact in a clinic sample of multiple sclerosis patients.* **Archibald, CJ, et al.** s.l. : Wolters Kluwer, 1994, Pain, pp. 89-93.
18. **Deloitte.** *The cost of pain in Australia.* s.l. : Deloitte Access, 2019.
19. **Werfel, PB, RE, Fanco Duran and LJ, Trettin.** *Multiple Sclerosis Advances in Psychotherapy – Evidence-Based Practice.* s.l. : Hogrefe Publishing, 2016. pp. 120-121.
20. *Pain in multiple sclerosis: a systematic review of neuroimaging studies.* **Seixas, D, et al.** s.l. : Elsevier, July 5, 2014, NeuroImage: Clinical, Vol. 5, pp. 322-331. 2014.06.014..
21. *Systematic assessment and characterization of chronic pain in multiple sclerosis patients.* **Ferraro, D, et al.** 3, Modena : Springer, Marcg 2018, Neurological Sciences: official journal of the italian neurological society, Vol. 39, pp. 445-453. 10.1007/s10072-017-3217-x.
22. *Multiple Sclerosis-Related Pain Syndromes: An Imaging Update.* **Mazhari, A.** 12, Ohio : Springer, December 2016, Vol. 20, p. 63.
23. *An Empirical Investigation of a Biopsychosocial Model of Pain in Multiple Sclerosis.* **Day, MA, et al.** 2, s.l. : Wolters Kluwer, February 2016, The Clinical Journal of Pain, Vol. 32, pp. 155-163.
24. *The Prevalence of Pain in Adults with Multiple Sclerosis: A Multicenter Cross-Sectional Survey.* **Drulovic, J, et al.** 8, s.l. : Oxford Academic, Pain Medicine, Vol. 16, pp. 1597-1602.
25. *Multiple sclerosis-induced neuropathic pain: pharmacological management and pathophysiological insights from rodent EAE models.* **Khan, N and Smith, MT.** 1, s.l. : PMC, February 20014, Inflammopharmacology, Vol. 22, pp. 1-22.
26. *Pain associated with multiple sclerosis: systematic review and proposed classification.* **O'Connor, AB, et al.** s.l. : Wolters Kluwer, July 2008, Pain, pp. 96-111.