Annex 3

VILNIUS UNIVERSITY

MEDICAL FACULTY

The Final thesis

Spasticity in Multiple Sclerosis- medical treatment options

Student **Stefanie, Tanja Reutter, VI year, 3 group**

Department/ Clinic (where the defence procedure will be taking place) - **Department of Rehabilitation, Physical and Sports Medicine**

Supervisor Lect. Jurate Kesiené

(academic and scientific degree name surname)

Consultant (if applicable) _____

The Head of Department/Clinic Prof. Dr. Tomas Aukstikalnis

(academic and scientific degree name surname)

Student email stefanie.reutter@mf.stud.vu.lt

Table of Contents

1. Abbrevations

- MS = Multiple Sclerosis
- MRI = Magnetic Resonance Imaging
- GABA = gamma aminobutyric acid
- FDA = Food and Drug Administration
- THC = Tetrahydrocannabinol
- CBD = Cannabidiol
- EQVAS = Experience-based health state evaluation score
- NRS score = numeric rating scale

2. Summary

Multiple Sclerosis is a chronic auto inflammatory disease of the central nervous system. The disease has a wide range of symptoms depending on the area affected in the brain.(11) Spasticity is one of the most prevalent symptoms in patients with MS. There are certain problems that arise in the treatment of spasticity. Many patients experience severe side effects because of multimedication and treatment resistant spasticity appears to be a huge problem in patients.(1)(11)(48) With a new syndrome called Spasticity plus syndrome, problems like multimedication, severe side effects and other arising problems could be cured. A few pharmacological treatment options are available, including the typical antispastic agents tizanidine, baclofen, and diazepam. The off-label use of Gabapentin. Furthermore, botulinum toxin injection is a newer treatment option. Cannabinoid oral mucosal spray is used as add on therapy for spasticity in MS which is becoming more popular. (54)

This systematic review aims to evaluate the efficacy and safety of different medical treatment options of spasticity in Multiple Sclerosis. Is the current available medical treatment of spasticity effective and safe for patients with MS and are there any new medical options for the future? After analyzing various articles and clinical trials, inconsistent effectiveness of different medical treatment options was seen. All medications like baclofen, tizanidine or oral mucosal cannabinoid spray had a positive effect on spasticity symptoms. Overall, the medical

treatment for spasticity in MS is showing good results. But additional the burden of side effects is huge.

3.Introduction

Multiple Sclerosis is a chronic inflammatory autoimmune disease of the Central nervous System. Worldwide more than 2.5 million people are affected by the disease. The clinical picture has a wide range depending on the areas affected in the brain. The disease is characterized by a delay of nerve conduction due to demyelination of nerve fibers and neuronal damage. The causes of the disease are multifactorial and lead to neurodegeneration of the Central nervous system.

Spasticity is one of the most common symptoms and affects about seventy eight percent of patients with Multiple Sclerosis. (11) Spasticity is referred to muscle stiffness or tightness and defined as a velocity-dependent increase in muscle tone. The quality of life of patients with spasticity symptoms in Multiple Sclerosis is diminished and daily life activities are severely affected. The treatment of spasticity in Multiple Sclerosis is symptomatic and has a wide range of options. Multimedication because of a wide range of symptoms at the same time lead to severe side effects, drug interactions or worsening symptoms. Treatment resistant spasticity symptom is another arising problem for patients and physicians. (1)(11)(48) The newest study results have shown positive effects in the treatment of spasticity symptoms with oromucosal cannabinoid spray. Furthermore, the improvement of other symptoms of Multiple Sclerosis by oral mucosal cannabinoid spray were seen as well. That fact gave rise to the hypothesis of a new approach for the symptomatic treatment of Multiple Sclerosis and especially spasticity symptom. A broader concept is introduced called Spasticity Plus Syndrome. This broad concept would make it possible to manage a cluster of symptoms at the same time with only one drug, because they arise from the same pathophysiological process. This narrative review addresses newly arising information and study results in the treatment of spasticity in Multiple Sclerosis and its management. (1)(3)(39)(40)(49)(50)

4. Literature search strategy

This article is a narrative review. All articles with related topics were collected and screened. PRISMA, preferred items for systematic reviews and meta-analysis were used to report the

results of this literature review. The databases used for the search included Google Scholar, PubMed, Medline, Sage Journals and Cochrane data Base. The following keywords and search phrases were used: ‘’Spasticity in MS’’, ‘’MS treatment’’’, ‘’Spasticity treatment’’, ‘’Spasticity plus Syndrome’’’, ‘’spasticity cannabinoid treatment’’.All articles were screened with a standardized collection tool before inclusion.

4.1 Inclusion and Exclusion criteria

The exclusion criteria were Comments, letters, conference abstracts or posters, Studies including children (<18years of age), Studies not available in full text, Studies reporting about Phase 1 or 2 Phase trials drugs.

Study selection

To exclude eligible articles from the screening, all articles were reviewed. To avoid the risk of bias across studies or within one study, the design of the study as well as the methodology and selection of participants was evaluated.

4.2 Results

With the keywords mentioned above 139.282 articles were identified after searching the named databases. (127.000 google scholar, 9080 pubmed, 32 medline, 2872 sage journals, 289 cochrane database) After exclusion criteria like not full text available, comments, letters and others mentioned above, 26.080 articles remained. (google scholar 17.600, pubmed 8000, sage journals 372, cochrane database 108) The article selection is shown in the PRISMA chart.

Prisma Chart Table

Identification

Identified records through Databases (n = 139 282)	Google scholar (n=127 000) Pubmed (n=9080) Sage journals (n=2872) Medline (n=32) Cochrane (n=289)

Screening

Screened articles (n=26.080) Google scholar (n=17.600) Pubmed (n=8000) Sage journals (n=372) Cochrane database (n=108)	Exclusion criteria Inclusion criteria

Eligibility + Included

Full text articles screened (n=57)

4.3 Quality Assessment

With the studies used for this review, there might be a risk of bias. Most of the studies used questionnaires to evaluate the quality of life and severity of spasticity. With this fact the risk of response bias is very high. Selection bias is also a risk, because selection of treatment groups is not randomized, if supervisors can decide which patient group receives which treatment. Furthermore, reporting bias in studies, where the outcome only mentions the significant results, but not the less significant results of the study. Comparability can also be limited, when evaluating the different types of assessment tools that are used to evaluate the results of the studies. For most of the studies included, standardized assessment scales were used, like the Modified Ashworth scale. And the participants included in the study had a wide range of Multiple Sclerosis types included into the studies, as well as wide range of age groups and no standardized treatment plan before being part in the study. Another fact is that some studies do not include a control group. When interpreting the results of this narrative review, the mentioned limiting factors should be considered.

5. Clinical presentation of Multiple Sclerosis

Multiple Sclerosis is also known as disseminated encephalomyelitis, which is a chronic inflammatory autoimmune disease of the Central nervous System. (1) The term multiple sclerosis originates from the Latin word ‘’multiple’’, which signifies ‘’numerous’’ and the Greek word ‘’skleros’’meaning ‘’hard’’. Worldwide there are approximately 2,5 million people affected, meaning MS is the most prevalent chronic inflammatory autoimmune

disease of the Central nervous System. (51)(53) The complex genetic profile of a first-degree relativ of a person affected by Multiple Sclerosis faces a 20 to 40 times higher risk developing this condition. The disease Multiple Sclerosis arises from various factors including genetics, environmental and immune system. But the exact cause remains elusive and a complex interplay of various factors leads to the onset of the disease. As already mentioned, there is a genetic predisposition to develop Multiple Sclerosis, but until now no gene has been identified to be the primary cause. Certain environmental factors including low Vitamin D levels , smoking, viral infections with Eppstein-Barr Virus seem to trigger the development of the disease.(11)(16)(31) It is hypothised that in individuals with a genetic predisposition environmental factors, mentioned above provoke a dysregulation of the immune system, especially the T-cells, which may target the myelin sheet and lead to the typical lesions in Multiple Sclerosis. The disease has a wide variety of symptoms depending on the location of the lesion. There are no specific symptoms for the disease. Often visual disturbances resulting from optic nerv neuritis are symptoms of an initial manifestation. A typical sign of Multiple Sclerosis is weakness of muscles or paralysis , which results in coordination, balance and walking difficulties.(54)(51)Tingling or numbness in any body part, especially the limbs or other sensory changes are also common. Two thirds of Multiple Sclerosis patients have bladder dysfunction or bowel dysfunction, which leads to incontinence, diarrhea or obstipation. (51) Muscle stiffness and spasticity or chronic pain, which is sharp and stabbing, is another common symptom of Multiple Sclerosis and affects the daily life of these patients. (54) Cognitive and emotional changes , like mood swings, depression, anxiety, concentration and memory impairment or speech and swallowing difficulties are other symptoms of Multiple Sclerosis. Overall, it is important to mention that symptoms vary in severity, combination and duration. Not all individuals will develop all symptoms and symptoms can fluctuate. (2)(11)(16)(31)(32)(51)

5.1 Mechanism and Pathology

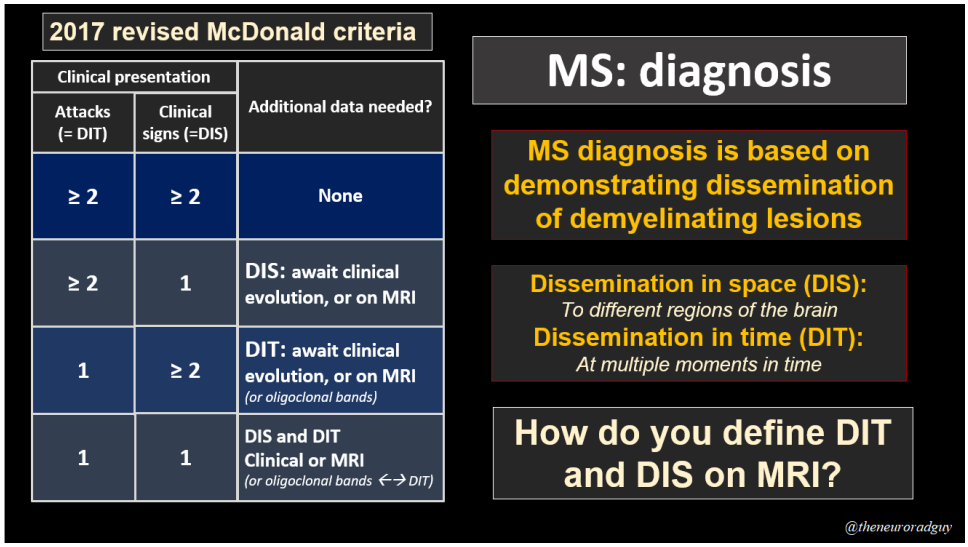
The pathology of Multiple Sclerosis is a combination of various factors including inflammation, demyelination, remyelination, neurodegeneration and gliotic scarring. (54) Severity and distribution through the Central nervous system vary among individuals, which leads to a wide variety of clinical manifestations. (51)

T and B-cells infiltrate the Central nervous System and activate macrophages and other inflammatory mediators leading to inflammation. Demyelination is a hallmark feature of

Multiple sclerosis, which is the loss of the protective myelin sheet of nerve fibers. Demyelination leads to an interrupted conduction of nerve impulses. Remyelination by oligodendrocytes happens as a response to demyelination with the goal of repairing nerve function, but this process is only partially effective. (51) Over time the processes of inflammation and demyelination lead to neurodegeneration, meaning more and more neurological deficits appear in response to ongoing damage of myelin sheets and nerve fibers. As a response to tissue damage in the Central nervous System reactive gliosis takes place. The gliosis process involves proliferation and activation of glial cells, especially astrocytes forming scar tissue. (11)(16)(32)(51)

5.2Diagnosis

The diagnosis of Multiple sclerosis is a diagnosis of exclusion and very complex involving several steps. The initial suspicion is based on a thorough clinical evaluation including the patients' medical history and family history, as well as a neurological examination. The Mc Donald criteria are used to determine the diagnosis of Multiple Sclerosis, which is shown in the table below. (51)



Picture 1: Mc Donald criteria (FgjNNPdX0AA3qXk.png:large)

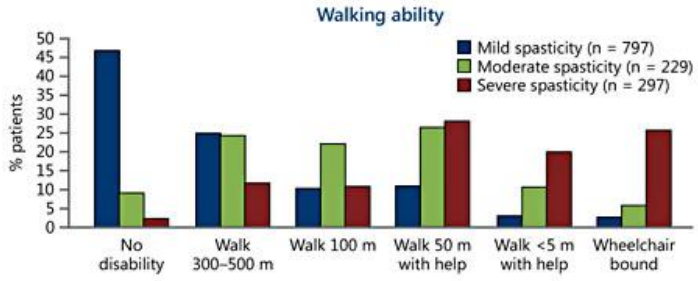
The Mc Donald criteria are updated by the International Panel on Diagnosis of Multiple Sclerosis. These criteria include the presence of certain clinical symptoms and certain laboratory findings and Magnetic Resonance Imaging results.(51)

The diagnosis of Multiple sclerosis remains mainly clinical. Good competence of the neurologist is needed to exclude other neurological conditions and show dissemination in

time and space. (54) On Magnetic Resonance Imaging (MRI) multilocular lesions in gray and white matter can be seen. These lesions are mostly located supra- or infratentorially, juxtacortically or periventricular. With cerebrospinal fluid analysis potential differential diagnoses can be ruled out and furthermore have a high prognostic value. (51) Multiple Sclerosis is a disease with an unpredictable and individual course of the disease. Age of onset, type of MS, initial symtpoms and response to treatment play a role when estimating the course of the disease. In general, it is said that the life expectancy for a person with Multiple Sclerosis may be reduced by 6-7 years, but it varies due to comorbidities and other things. (1)(2) (11)(16) (31)(32)(48)(51)

6.Spasticity in MS

Spasticity is one of the most common symptoms in Multiple Sclerosis. Different studies have shown that spasticity belongs to the most often appearing and most disabling symptoms in Multiple Sclerosis.(16)(20) It affects about 78% of patients with Multiple Sclerosis. It is a sign of the upper motor neuron syndrome which results from lesions in the brain or spinal cord. Typically, it leads to a velocity-dependent increase in muscle tone and therefore is referred to as muscle tightness or stiffness. (1)(20)(21) It can affect all four limbs of the body, but the impact on lower limbs of spasticity is much higher. (2) Spasticity severely impacts the daily life of patients with Multiple Sclerosis. Especially the mobility, walking and balance are affected, when lower limbs of the patients are affected by spasticity symptoms. There is a strong correlation between walking ability and spasticity severity, which is highlighted in the table below. (3)



Picture 2 : Walking ability (Oreja-Guevara C, González-Segura D, Vila C: Spasticity in multiple sclerosis: results of a Spanish patient survey. Int J Neurosci 2012;123:400-408.)

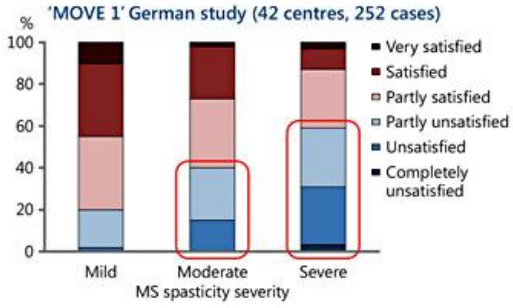
The table clearly shows that patients with severe spasticity are mainly wheelchair users, compared to patients with mild spasticity showing no disabilities or mild decrease in walking

distance. (3) Spasticity may also predict future falls. In a pilot investigation with 39 participants the correlation between lower limb spasticity and falls in individuals with Multiple Sclerosis was evaluated. One part of the participants were fallers, and the other part were non-fallers. Correlation coefficients between the number of falls and spasticity scores showed moderate association. P-values smaller than 0.05 indicated strong correlation. For example, the degree of spasticity of the ankle plantar flexor muscle group of fallers was significantly higher than in non-fallers with a p-value of 0.009. The correlation between other muscle groups' spasticity and falls was less significant. This cross-sectional study included 35 patients with Multiple Sclerosis and aimed to examine spasticity of lower limbs and their effect on gait and balance. Hipp adductors, knee extensors and plantar flexors were the muscle groups included. Four physiotherapists evaluated spasticity with bilateral tests of lower limb muscles with Modified Ashworth scale. In addition, the Two-Minute Walking test was used to measure gait. Habitual assistant devices were allowed to be used. And the Mini-Balance Evaluation system Test was used to measure different aspects of dynamic balance using 14 tasks. The participants were between 24 and 68 years of age with no significant differences in age or sex. (P-value= 0.432) The participants had mostly relapsing-remitting Multiple Sclerosis with a mean time since diagnosis of 12 years. Spasmolytic medication, mostly baclofen and other treatment options, were used by the participants. The study revealed a strong correlation between gait, balance and spasticity. This was identifiedd by the measurement results of this study.

For each increase in the level of spasticity, Modified Ashworth Scale scores decreased by one or more points. These results indicate that mobility is negatively affected by spasticity. Especially spasticity in the ankle muscles disturbs gait already in early stages, even when spasticity symptoms are not severe. On the other hand, moderate to severe spasticity in theproximal muscles has negative effects on gait and balance. With this cross-sectional study type it can be difficult to interpret the results, because other disturbances like vestibular, visual or proprioceptive symptoms of the participants were not specifically tested. This could bias the results of the study by other Multiple Sclerosis symptoms. (4) During physical examination it is seen, that the resistance increases the faster a muscle is moved or stretched.

For evaluation of the severity of spasticity the Modified Ashworth Scale is used most frequently with a grading scale from zero to four. (41)(42) In different papers it was mentioned that there is a dilemma in defining and measuring spasticity. The Ashworth Scale is a widely used tool but has limitations. These include the lack of comprehensive movement,

the failure to include dynamic measure, when spasticity is measured with change of position. Knowing about the failure of sensitivity of Modified Ashworth Scale in measuring spasticity, might be a problem in clinical trials. It can become a problem to illustrate the efficacy of a new treatment method. Despite criticism of the Modified Ashworth Scale it is used in most of the studies or Clinical trials, because it is the only accepted measurement scale to measure spasticity. (5)(17)(18) Evidence shows a limited effect of first line treatment for spasticity. The first line treatment includes medications like baclofen, tizanidine or gabapentin. In a German survey it was reported that physicians are completely unsatisfied with the treatment outcome of their patients in 40%. (6) The effect of first line treatment is shown in the table below.



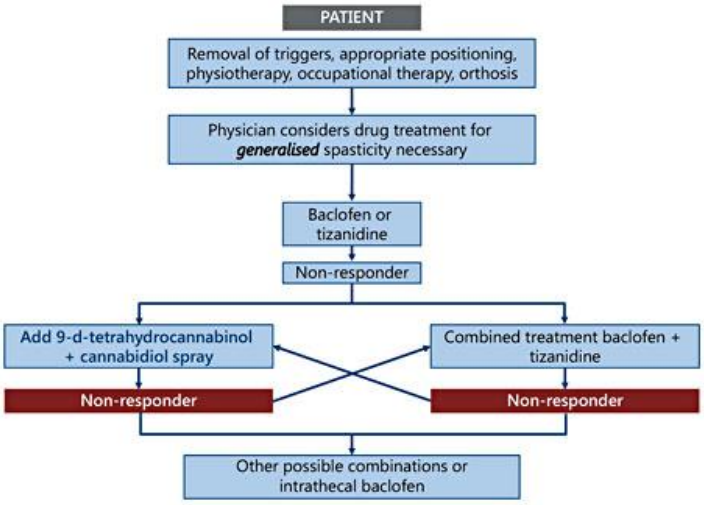
Picture 3: MS Spasticity severity (Oreja-Guevara C, González-Segura D, Vila C: Spasticity in multiple sclerosis: results of a Spanish patient survey. Int J Neurosci 2012;123:400-408.)

7.Treatment of spasticity

The treatment of spasticity aims to decrease muscle stiffness and improve the quality of life of patients with Multiple Sclerosis. Besides medication, physical therapy and assistive devices are used to improve the quality of life of patients. (20)(21)(30) The treatment of spasticity in Multiple Sclerosis is a symptomatic treatment and can worsen other symptoms or lead to side effects. Especially the polytherapy with many different drugs for different symptoms can lead to severe drug interactions and worsen symptoms.

That is why an appropriate treatment of symptoms in Multiple Sclerosis is an unmet need. For Multiple Sclerosis spasticity treatment, there are a few antispastic agents used. (8) Pharmacological first line treatment for generalized spasticity symptoms in Multiple Sclerosis include Baclofen, Tizanidine and Gabapentin. Second line pharmacological treatment includes Dantrolene and Diazepam. Additional added cannabinoid oral mucosal spray is third line therapy. Fourth line treatment includes baclofen pump and botulinum toxin injections

are used for focal spasticity. (54)



Picture 4 Treatment recommendations MS

(Oreja-Guevara C, González-Segura D, Vila C: Spasticity in multiple sclerosis: results of a Spanish patient survey. Int J Neurosci 2012;123:400-408.)

7.1 Baclofen

Baclofen is the drug of choice for MS induced spasticity. It is a GABA agonist and increases the inhibitory effect of the reflex pathway. It has a wide range of side effects including sedation, gastrointestinal symptoms, drowsiness, insomnia, tremors and confusion.(52) With long-term use of baclofen side effects like sedation and drowsiness can lower, because tolerance develops with time. Baclofen may also lower seizure threshold. (23)(24)(25)

Baclofen is usally taken orally with a dosis of 5mg /2x day to start with and can be adjusted in dosage every three to five days to a limit of 80mg/day. In patients with renal failure , dosage should be adjusted, because it has renal metabolism. Sudden withdrawal of the drug should be avoided, because it can cause severe symptoms with fever, seizures and death and rebound spasticity or hallucinations. (12)(15) The mentioned side effects can be reduced by starting a low-dose therapy with baclofen. (52)

Overdosing of baclofen leads to somnolence, hypotonia, respiratory depression, seizures and severe weakness. (22)(23)(24)(25)

Alternatively, an intrathecal baclofen pump with direct delivery of the drug to the cerebrospinal fluid is possible. A baclofen pump is a more invasive procedure and only used in severe cases. In patients with severe spasticity and a lack of tolerance or missing efficacy of less invasive treatment options, a baclofen pump can be placed subcutaneously within the abdominal wall. The ratio of drug concentration is one hundred to one at spinal cord level, compared to oral use. Careful monitoring and regular supervision are mandatory, when using

a baclofen pump for the treatment of spasticity. (9) (46)(47) Intrathecal baclofen administration is indicated for severe spasticity of both legs. Positive effects especially in reducing spasticity of legs and trunk. This furthermore has a big impact on posture, gait, independence and bladder function. The use of a baclofen pump has a positive effect directly at the spinal cord level for reducing spasticity symptoms. And more important, it has fewer side effects, because of lower levels of baclofen in the brain. (52)

7.2 Tizanidine

Tizanidine is an alpha-2 adrenergic agonist. Sedation and drowsiness are the most common side effects. Others include liver damage, bradycardia, hypotension, dry mouth and dizziness. (33) Tizanidine reduces muscle tone. Tizanidine inhibits presynaptic motorneurons.(52) In a double-blind placebo controlled clinical trial from 2016 by Y. Lapierre the safety and efficacy of tizanidine treatment for spasticity in MS patients was evaluated. It showed tizanidine to be a safe and effective drug in the treatment of spasticity. The most common and only side effects were dry mouth and drowsiness. Thats why the clinical trial states the drug to be safe and effective. Tizanidine has a clear effect on tendon reflexes and muscle tone. (8)(19)

The drug is metabolized by the liver. Because of cytochrome P450 inhibition it is contraindicated to use together with intravenous ciprofloxacin. Liver function tests are mandatory on a regular basis. When taken together with antihypertensive drugs, special attentiveness is necessary. (52) Two to four milligram per day typically taken at bedtime is the dose to start with. A dose of thirty-six milligrams per day is the maximum dose allowed. (9) (26)(27)(28)(29)(33)

7.3Diazepam

Diazepam is an antispasmodic agent promoting the effect of GABA (gamma-aminobutyric acid). This neurotransmitter has an inhibitory effect. Diazepam has the most sedating effect and is metabolized by the liver. Risk of Central nervous system depression is high, when it is taken together with alcohol. (9) (23) Evidence for the use of diazepam for spasticity symptoms is very low. Therefor diazepam should not be prescribed as a first line medical treatment for spasticity in MS. (52)

7.4 Gabapentin

Gabapentin is an antiepileptic drug that is used off-label for the treatment of some symptoms in Multiple Sclerosis. Usually, it is used for seizures in epilepsy. The symptoms in MS treated with gabapentin include nerve pain, dyesthesias, spasticity and vision problems. Dosage usually is adjusted according to the effect of symptom relief and apprearance of side effects. (56) Clinical trials with gabapentin used for the treatment of spasticity in spinal cord injury showed small improvement of symptoms. Ashworth scale scores improved also. Gabapentin is a drug with well-known side effects and good tolerability, which is known from the use in epilepsy patients. Doses of 900mg a day were used to treat the probands, with only a little effect. High doses might be needed to treat spasticity and get good results and symptom relief. (57) As Gabapentin is only used off-label for the treatment of spasticity in MS patients, there are not many clinical trials or systematic reviews. Further studies are needed to investigate the effect of gabapentin for the treatment of spasticity in MS.(56)

7.5 Botulinum Toxin

Botulinum Toxin injection is indicated in MS if other medications don't reduce spasticity symptoms. Also, when the daily live activity is severely impaired by muscle spasticity. (14) There are five agents approved by the FDA for treatment of spasticity, both type A and B Botulinum toxin. All agents function at the neuromuscular junction site by blocking the presynaptic release of acetylcholine. (43)(44)(45) The current botulinum toxins medications on the market are all made of botulinum clostridium bacteria. Botulinum toxin inhibits the acetylcholine release at the neuromuscular junction. Muscle contractions are reduced. Muscle strength is decreased dosage related. Degradation of the injected botulinum toxin leads to a reversible improvement of spasticity symptoms. (14)

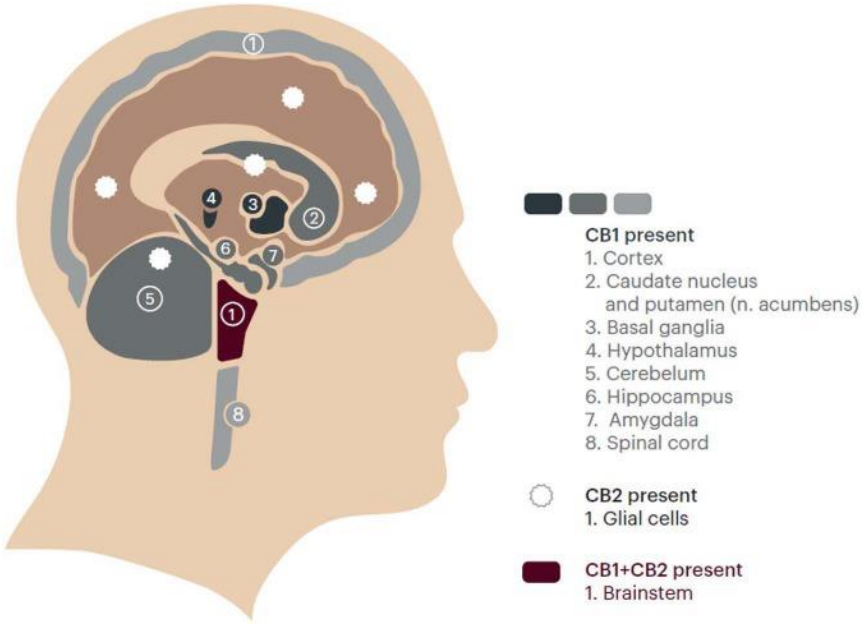
Botulinum toxin should be used as a first line treatment in patients with spasticity, especially with impaired quality of life. Proper implementation of botulinum toxin in the initial stage of rehabilitation can improve quality of life of patients and reduce consequences of spasticity. Soft tissue atrophy can be reduced with early implementation of botulinum toxin for spasticity treatment. (52) Still unknown is the maximum saturation of different muscles for botulinum toxin injections and therefore the maximum dose allowed. In different studies it was mentioned that an exact localization for the injection site is mandatory. Furthermore, to calculate the doses for injection, further investigation with clinical trials is needed. For the exact localization of injection site, it might be helpful to use electrostimulation. (14)

Another problem arising is the theory of maximum saturation of botulinum toxin of a muscle. This theoretical knowledge leads to the question of how many injections per muscle are needed to spread the toxin to the whole muscle and get the full effect. (52)

The effect of botulinum toxin slightly build up after 4-6 days and last up to 16 weeks. Side effects include muscle atrophy at injection site. During the first 3 weeks the botulinum syndrome can appear, which includes asthenia or generalized muscle weakness. In patients with anticoagulation therapy the risk of developing muscle hematoma at the injection site should be monitored. (52) Further studies on long term efficacy of botulinum toxin need to be done. (14)

7.6 Cannabinoid oral mucosal spray

New study results have been evaluating the effect of newly implemented cannabinoid oral mucosal spray in MS patients, especially for spasticity symptom relief. Most of them have treatment resistant spasticity and severe reduction of quality of life. It is known that Cannabinoid receptors are located randomly in the central nervous system and especially in the brain stem they are accumulated. The cannabinoid system of the brain is shown in the picture above. The cannabinoid receptors CB1 and CB2 are scattered through the central nervous system. In one area of the brain there is a high accumulation of CB1 and CB2 receptors, which is the brainstem. The brainstem mediates symptoms like bladder function, sleep, spasticity and more. CB1 receptors are widely spread in the brain and are related to areas linked to movement, memorys, sensory perception and appetite and endocrine function and more. CB2 receptors interfere with cytokine release and regulate imune cells. This plays an important role in autoinflammatory processes and reduces inflammation. (48)



Picture 5 Cannabinoid receptor localizations in brain (Fernández Ó, Costa-Frossard L, Martínez-Ginés M, Montero P, Prieto JM, Ramió L. The Broad Concept of "Spasticity-Plus Syndrome" in Multiple Sclerosis: A Possible New Concept in the Management of Multiple Sclerosis Symptoms. Front Neurol. 2020 Mar 17;11:152. doi: 10.3389/fneur.2020.00152. PMID: 32256440; PMCID: PMC7090019.)

Different clinical trials and studies have shown that oral mucosal cannabinoid sprays like Nabiximols have a positive effect on reducing symptoms of spasticity and others in Multiple Sclerosis patients, that are resistant to other medical treatment options.

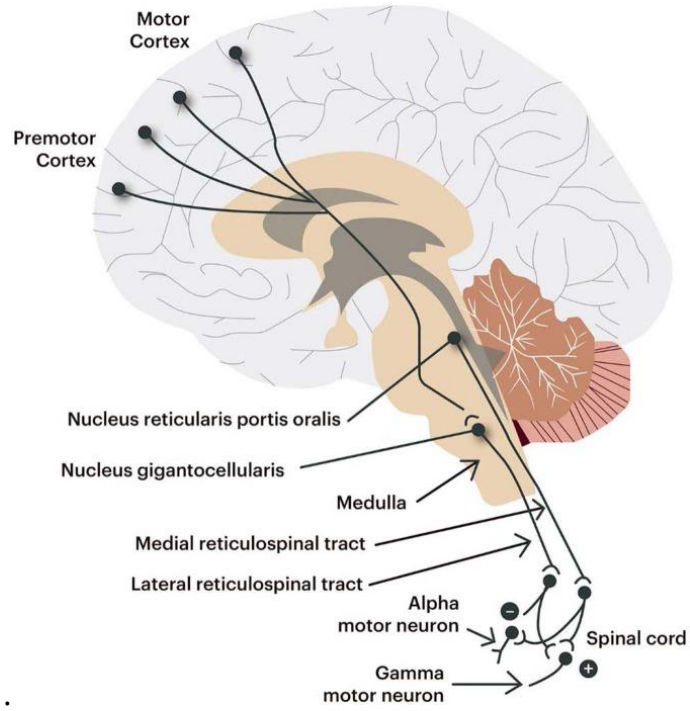
Nabiximols are made from the Cannabis sativa plant extracts, and it has equal amount of Tetrahydrocannabinol (THC) and Cannabidiol (CBD). Oro mucosal administration route has a longer duration and slower onset of action, because of the high lipophilicity of Cannabis. For example, inhalation medicine has a short duration and fast onset of action. (2)(13) In a retrospective study from Belgium with 238 probands the effect of oromucosal cannabinoid spray on spasticity symptom was evaluated. The NRS spasticity scale from 0 to 10 points, Experience-based health state evaluation score (EQVAS score), and dosage were reported. Patients' outcomes were collected at baseline, 4, 8, 12 weeks and further supervised at 6, 9 and 12 months. During the whole evaluation period the dosage of 6 sprays/day was stable. The Experience-based health state evaluation score (EQ VAS score), to measure the health-related quality of life scored from 0 to one 100, was improving over the complete period of 12 months from a baseline result of 39 points to 64 points after 12 months. Results of the NRS spasticity scale improved of more than 20 percent after 4 weeks of therapy with oromucosal cannabinoid spray. (2)

Another Italian study with similar results talks about cannabinoid oromucosal spray as a useful option for patients with Multiple Sclerosis. 70.5 percent of the probands had more than 20 percent improvement of symptoms as initial response. The mean NRS score improved from 7.5 to 5.8, that is a 22.6 percent improvement. (34)(35)(36)(37)(38)(39)(40)

7.7 Spasticity Plus syndrome

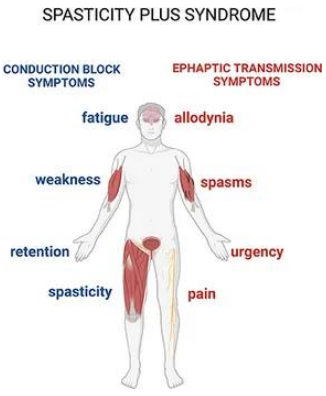
The results of the studies with oromucosal cannabinoid spray also showed improvement of other symptoms like cramps, bladder dysfunction, sleep, tremor and more. This indirect information gave rise to the hypothesis of Spasticity Plus syndrome. This theory states that all signs and symptoms accompanying spasticity are a cluster of clinical manifestations with one underlying pathophysiology. (48) A group of neurologists specialized in Multiple Sclerosis assed the symptoms of patients and especially the symptom clustering in MS. Muscle cramps and bladder dysfunction were associated mostly with spasticity symptom. Through the course of MS disease, the Spasticity Plus syndrome can become clearer.(55) This would propose a new approach to treat spasticity in Multiple Sclerosis. The Poly pharmaceutical approach to treat Multiple Sclerosis patients leads to the higher risk of side effects and the overall loss of the disease process. For clinicians the Spasticity Plus Syndrome could shift the focus to a whole cluster of symptoms away from spasticity only. (49) The underlying pathophysiology of Spasticity Plus Syndrome is said to be placed in the corticospinal tract. Anatomically the corticospinal tract is divided into a direct and crossed corticospinal tract. The fibers, which are responsible for the stretch reflex lie in the crossed corticospinal tract and reach gamma motor neurons. The fibers responsible for voluntary movement are in the direct corticospinal tract and reach alpha motor neurons. In Multiple Sclerosis both pathways are interrupted, not only one.

The symptom of spasticity without weakness only appears when a selective interruption of the crossed (lateral) corticospinal tract is seen.



Picture 6 Pathway Corticospinal tract(Fernández Ó, Costa-Frossard L, Martínez-Ginés M, Montero P, Prieto JM, Ramió L. The Broad Concept of "Spasticity-Plus Syndrome" in Multiple Sclerosis: A Possible New Concept in the Management of Multiple Sclerosis Symptoms. Front Neurol. 2020 Mar 17;11:152. doi: 10.3389/fneur.2020.00152. PMID: 32256440; PMCID: PMC7090019.)

Further the study hypothesizes that due to the fact of smaller fibers of lateral corticospinal tract, they are more sensitive to demyelination effect and have higher sensitivity to conduct blocks. This conduction blocks lead to an easy ephaptic transmission to close surrounding fibers. These conduction blocks could be the origin of negative symptoms of Spasticity Plus syndrome. These negative persisting symptoms include fatigue, weakness and urinary retention.



Picture 7 : Spasticity Plus syndrome (Fernández Ó, Costa-Frossard L, Martínez-Ginés M, Montero P, Prieto JM, Ramió L. The Broad Concept of "Spasticity-Plus Syndrome" in Multiple Sclerosis: A Possible New Concept in the Management of Multiple Sclerosis Symptoms. Front Neurol. 2020 Mar 17;11:152. doi: 10.3389/fneur.2020.00152. PMID: 32256440; PMCID: PMC7090019.)

These demyelinated fibers could also propagate excitation to close surrounding damaged fibers and cause ephaptic symptoms like pain, allodynia, spasms and more. As demyelinated fibers which are close to each other share the same extracellular medium, this transmission can take place. (48)(49) The picture above shows the characteristics of the Spasticity Plus syndrome. The syndrome includes the conduction bock symptoms and on the other hand ephaptic transmission symptoms. These ephaptic symptoms come from propagation of nerve impulses of demyelinated fibers to close surrounding damaged fibers. In healthy people the myelination of nerve fibers would prevent the excitation of impulses to clos surrounding nerve fibers.(48)

8.Conclusion

Multiple Sclerosis is a chronic inflammatory autoimmune disease of the central nervous system affecting a lot of people worldwide. It has a broad spectrum of symptoms. Spasticity belongs to the more common symptoms and has a huge impact on the quality of life. The treatment options often have only a little effect. Side effects are common and due to multimedication drug interactions worsen the situation of Multiple Sclerosis patients. First line pharmacological treatment with baclofen or tizanidine shows good results in reducing spasticity symptoms. To reduce the side effects, appropriate dosage is important and regular supervision of the treatment. (1)(53)(54) The second line treatment option with diazepam is less effective and should not be a drug of first choice. Side effects are the main problem and the positive effect of the drug to reduce spasticity symptoms are too little.(9)(23)(52) New treatment options for spasticity with add on cannabinoid oral mucosal spray have already shown positive results. Spasticity symptoms improved and patients reported a better quality of life. Due to the wide spread of cannabinoid receptors throughout the brain and high amount of CB1 and CB2 receptors in the brain stem, the effect of cannabinoid oral mucosal spray in reducing spasticity is good.(34)(35)(36) Botulinum toxin injection as fourth line treatment options for severe cases of spasticity or spasticity of both legs or the trunk has shown good results. The early implementation can reduce muscle atrophy and improve rehabilitation and quality of life and independence of patients suffering from spasticity in Multiple Sclerosis. But further clinical trials are needed to investigate the treatment with botulinum toxin. Maximum dosage might be restricted because of muscle drug saturation, but this fact has not been evaluated with clinical trials. Also, the longterm efficacy of botulinum toxin injection needs to be evaluated.(43)(44)(45)(52)

With the implementation of Spasticity plus Syndrome clustering of symptoms could be treated with one drug. The Spasticity Plus syndrome could be a new approach for the treatment of Multiple Sclerosis and reduce multidrug treatment. This new approach could reduce drug interactions, side effects and shift the focus of physicians to a whole cluster of symptoms that need to be treated. Clustering of MS symptoms in patients is common and includes mostly spasticity being one of them, paired with bladder dysfunction or others. (48)

Overall, the treatment of Multiple Sclerosis spasticity is an important part of this disease. With this systematic review different treatment options were discussed.

In general, the symptoms of MS vary from patient to patient and need individual treatment plans. The different medical treatment options like baclofen, botulinum toxin injection and others should be chosen individually for each patient depending on symptom severity. For patients with treatment resistant spasticity, add on therapy with cannabinoid oral mucosal spray could be a good choice. (53)(54) Clinical trials showed positive results in symptom reduction and safety of the drugs. Further studies for long-term efficacy and safety need to be done, which was mentioned equally in all studies.The newly implemented cannabinoid oral mucosal spray has an overall positive effect which was seen in all clinical trials. Comparing the results of the studies included, they all came up with a positive symptom relief for patients and no or only little side effects, compared to other drugs used. (48)(49) Especially the oral antispastic agents' baclofen, diazepam and tizanidine have good effects in reducing spasticity symptoms, but amount and severity of side effects is problematic. This result was seen in all reviews and clinical trials. Therefor the intervention of the spasticity plus syndrome could help to reduce drug interactions, side effects and improve quality of life for patients with MS in the future. (49)(55) Studies for the treatment with botulinum toxin had positive results for severe spasticity cases. But long-term efficacy and safety are not fully investigated, and studies have shown that further study results are needed to check for longterm effectiveness and dosage. These two points need further investigations. (43)(44)(45)

To summarize, studies and clinical trials have shown the problematic situation in MS patients with multidrug treatment and appearance of drug side effects. New interventions with cannabinoid oral mucosal spray and a new approach with spasticity plus syndrome could reduce the appearance of drug side effects and improve quality of life of patients. Additional positive effects of these new interventions are equally mentioned in all studies.

9. References

(1) (Carlo Pozzilli; Overview of MS Spasticity. *Eur Neurol* 1 January 2014; 71 (Suppl. 1): 1–3.)

(2) Zuhal Abasıyanık[1,2], Cavid Baba[1], Turhan Kahraman[2], Ozge Ertekin[4], Serkan Ozakbas[3], on behalf of Multiple Sclerosis Research Group

(3) (Oreja-Guevara C, González-Segura D, Vila C: Spasticity in multiple sclerosis: results of a Spanish patient survey. Int J Neurosci 2012;123:400-408.)

(4) Norbye AD, Midgard R, Thrane G. Spasticity, gait, and balance in patients with multiple sclerosis: A cross-sectional study. *Physiother Res Int*. 2020;25:e1799.

(5) MohanaSundaram A, Thukani Sathanantham S, Gudesblatt M, Ganvir S, Chinchole V, Patil B, Velayutham R. Using modified Ashworth scale for assessing multiple sclerosis-associated spasticity: a high time for a paradigm shift. Ther Adv Neurol Disord. 2023 Feb 18;16:17562864231154653. doi: 10.1177/17562864231154653. PMID: 36814810; PMCID: PMC9940219.

(6) Shakespeare DT, Boggild M, Young C: Anti-spasticity agents for multiple sclerosis. Cochrane Database Syst Rev 2003;4:CD001332.

(7) Oreja-Guevara C, Montalban X, de Andrés C, Casanova-Estruch B, Muñoz-García D, García I, Fernández Ó: [Consensus document on spasticity in patients with multiple sclerosis]. Rev Neurol 2013;57:358-373.

(8) Lapierre Y, Bouchard S, Tansey C, Gendron D, Barkas WJ, Francis GS. Treatment of Spasticity with Tizanidine in Multiple Sclerosis. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*. 1987;14(S3):513-517. doi:10.1017/S0317167100038026

(9) (Rivelis Y, Zafar N, Morice K. Spasticity. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from:

(10) Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manage. 2004 Aug;28(2):140-75. [PubMed]))

(11) Haki M, Al-Biati HA, Al-Tameemi ZS, Ali IS, Al-Hussaniy HA. Review of multiple sclerosis: Epidemiology, etiology, pathophysiology, and treatment. Medicine (Baltimore). 2024 Feb 23;103(8):e37297. doi: 10.1097/MD.0000000000037297. PMID: 38394496; PMCID: PMC10883637.

(12) Hassan N, McLellan DL. Double-blind comparison of single doses of DS103-282, baclofen and placebo for suppression of spasticity. J Neurol Neurosurg Psychiatry. 1980 Dec;43(12):1132-6. doi: 10.1136/jnnp.43.12.1132. PMID: 7217960; PMCID: PMC490787.

(13) Khan F, Amatya B, Bensmail D, Yelnik A. Non-pharmacological interventions for spasticity in adults: An overview of systematic reviews. Ann Phys Rehabil Med. 2019 Jul;62(4):265-273. doi: 10.1016/j.rehab.2017.10.001. Epub 2017 Oct 16. PMID: 29042299.

(14) Hui D, Argáez C. Onabotulinum Toxin A (Botox) for Spasticity Associated With Multiple Sclerosis [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2021 Mar. PMID: 34260163.

(15) Azouvi P, Mane M, Thiebaut JB, Denys P, Remy-Neris O, Bussel B. Intrathecal baclofen administration for control of severe spinal spasticity: functional improvement and long-term follow-up. Arch Phys Med Rehabil. 1996 Jan;77(1):35-9. doi: 10.1016/s0003-9993(96)90217-8. PMID: 8554471.

(16) Travers BS, Tsang BK, Barton JL. Multiple sclerosis: Diagnosis, disease-modifying therapy and prognosis. Aust J Gen Pract. 2022 Apr;51(4):199-206. doi: 10.31128/AJGP-07-21-6103. PMID: 35362004.

(17) Torres-Moreno MC, Papaseit E, Torrens M, Farré M. Assessment of Efficacy and Tolerability of Medicinal Cannabinoids in Patients With Multiple Sclerosis: A Systematic Review and Meta-analysis. JAMA Netw Open. 2018 Oct 5;1(6):e183485. doi: 10.1001/jamanetworkopen.2018.3485. PMID: 30646241; PMCID: PMC6324456.

(18) Luo Z, Lo WLA, Bian R, Wong S, Li L. Advanced quantitative estimation methods for spasticity: a literature review. *Journal of International Medical Research*. 2020;48(3). doi:10.1177/0300060519888425

(19) LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012–. Tizanidine. 2017 Jan 30. PMID: 31643379.

(20) Schapiro RT. Pharmacologic Options for the Management of Multiple Sclerosis Symptoms. *Neurorehabilitation and Neural Repair*. 2002;16(3):223-231. doi:10.1177/154596802401105162

(21) Guo X, Wallace R, Tan Y, Oetomo D, Klaic M, Crocher V. Technology-assisted assessment of spasticity: a systematic review. J Neuroeng Rehabil. 2022 Dec 9;19(1):138. doi: 10.1186/s12984-022-01115-2. PMID: 36494721; PMCID: PMC9733065.

(22) Hobart JC, Riazi A, Thompson AJ, Styles IM, Ingram W, Vickery PJ, Warner M, Fox PJ, Zajicek JP. Getting the measure of spasticity in multiple sclerosis: the Multiple Sclerosis Spasticity Scale (MSSS-88). Brain. 2006 Jan;129(Pt 1):224-34. doi: 10.1093/brain/awh675. Epub 2005 Nov 9. PMID: 16280352.

(23) Evidence review for pharmacologicalmanagement of spasticity: Multiple sclerosis in adults: management: Evidence review F. London: National Institute for Health and Care Excellence (NICE); 2022 Jun. PMID: 37459428.

(24) Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006–. Baclofen. 2019 Jun 3. PMID: 30000260.

(25) Ng L, Khan F, Young CA, Galea M. Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev. 2017 Jan 10;1(1):CD011776. doi: 10.1002/14651858.CD011776.pub2. PMID: 28072907; PMCID: PMC6469543.

(26) Zhu LL, Wang YH, Zhou Q. Tizanidine: Advances in Pharmacology & Therapeutics and Drug Formulations. J Pain Res. 2024 Mar 21;17:1257-1271. doi: 10.2147/JPR.S461032. PMID: 38529017; PMCID: PMC10962466.

(27) Bass B, Weinshenker B, Rice GPA, et al. Tizanidine Versus Baclofen in the Treatment of Spasticity in Patients with Multiple Sclerosis. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*. 1988;15(1):15-19. doi:10.1017/S0317167100027104

(28) Garg N, Smith TW. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. Brain Behav. 2015 Sep;5(9):e00362. doi: 10.1002/brb3.362. Epub 2015 Aug 3. PMID: 26445701; PMCID: PMC4589809.

(29) Intiso D, Simone V, Bartolo M, Santamato A, Ranieri M, Gatta MT, Di Rienzo F. High Dosage of Botulinum Toxin Type A in Adult Subjects with Spasticity Following Acquired Central Nervous System Damage: Where Are We at? Toxins (Basel). 2020 May 10;12(5):315. doi: 10.3390/toxins12050315. PMID: 32397674; PMCID: PMC7291232.

(30) Baecher-Allan C, Kaskow BJ, Weiner HL. Multiple Sclerosis: Mechanisms and Immunotherapy. Neuron. 2018 Feb 21;97(4):742-768. doi: 10.1016/j.neuron.2018.01.021. PMID: 29470968.

(31) Ransohoff, R., Hafler, D. & Lucchinetti, C. Multiple sclerosis—a quiet revolution. *Nat Rev Neurol* 11, 134–142 (2015).

(32) Huang WJ, Chen WW, Zhang X. Multiple sclerosis: Pathology, diagnosis and treatments. Exp Ther Med. 2017 Jun;13(6):3163-3166. doi: 10.3892/etm.2017.4410. Epub 2017 Apr 28. PMID: 28588671; PMCID: PMC5450788.

(33) Kamen L, Henney HR 3rd, Runyan JD. A practical overview of tizanidine use for spasticity secondary to multiple sclerosis, stroke, and spinal cord injury. Curr Med Res Opin. 2008 Feb;24(2):425-39. doi: 10.1185/030079908x261113. PMID: 18167175.

(34) Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses. 2006;66(2):234-46. doi: 10.1016/j.mehy.2005.08.026. Epub 2005 Oct 4. PMID: 16209908.

(35) Mecha M, Carrillo-Salinas FJ, Feliú A, Mestre L, Guaza C. Perspectives on Cannabis-Based Therapy of Multiple Sclerosis: A Mini-Review. Front Cell Neurosci. 2020 Feb 19;14:34. doi: 10.3389/fncel.2020.00034. PMID: 32140100; PMCID: PMC7042204.

(36) Chan A, Silván CV. Evidence-based management of multiple sclerosis spasticity with nabiximols oromucosal spray in clinical practice: a 10-year recap. Neurodegener Dis Manag. 2022 Jun;12(3):141-154. doi: 10.2217/nmt-2022-0002. Epub 2022 Apr 4. PMID: 35377770.

(37) Notcutt W, Langford R, Davies P, Ratcliffe S, Potts R. A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex® (nabiximols). Mult Scler. 2012 Feb;18(2):219-28. doi: 10.1177/1352458511419700. Epub 2011 Aug 30. PMID: 21878454.

(38) Kleiner D, Horváth IL, Bunduc S, Gergő D, Lugosi K, Fehérvári P, Hegyi P, Csupor D. Nabiximols is Efficient as Add-On Treatment for Patients with Multiple Sclerosis Spasticity Refractory to Standard Treatment: A Systematic Review and Meta-Analysis of Randomised Clinical Trials. Curr Neuropharmacol. 2023;21(12):2505-2515. doi: 10.2174/1570159X21666230727094431. PMID: 37519000; PMCID: PMC10616923.

(39) Celius EG, Vila C. The influence of THC:CBD oromucosal spray on driving ability in patients with multiple sclerosis-related spasticity. Brain Behav. 2018 Apr 6;8(5):e00962. doi: 10.1002/brb3.962. PMID: 29761015; PMCID: PMC5943754.

(40) Akgün K, Essner U, Seydel C, Ziemssen T. Daily Practice Managing Resistant Multiple Sclerosis Spasticity With Delta-9-Tetrahydrocannabinol: Cannabidiol Oromucosal Spray: A Systematic Review of Observational Studies. J Cent Nerv Syst Dis. 2019 Mar 11;11:1179573519831997. doi: 10.1177/1179573519831997. PMID: 30886530; PMCID: PMC6413425.

(41) Balci BP. Spasticity Measurement. Noro Psikiyatr Ars. 2018;55(Suppl 1):S49-S53. doi: 10.29399/npa.23339. PMID: 30692856; PMCID: PMC6278623.

(42) He J, Luo A, Yu J, Qian C, Liu D, Hou M, Ma Y. Quantitative assessment of spasticity: a narrative review of novel approaches and technologies. Front Neurol. 2023 Jul 5;14:1121323. doi: 10.3389/fneur.2023.1121323. PMID: 37475737; PMCID: PMC10354649.

(43) Picelli A, Santamato A, Chemello E, Cinone N, Cisari C, Gandolfi M, Ranieri M, Smania N, Baricich A. Adjuvant treatments associated with botulinum toxin injection for managing spasticity: An overview of the literature. Ann Phys Rehabil Med. 2019 Jul;62(4):291-296. doi: 10.1016/j.rehab.2018.08.004. Epub 2018 Sep 13. PMID: 30219307.

(44) Mihai EE, Popescu MN, Iliescu AN, Berteanu M. A systematic review on extracorporeal shock wave therapy and botulinum toxin for spasticity treatment: a comparison on efficacy. Eur J Phys Rehabil Med. 2022 Aug;58(4):565-574. doi: 10.23736/S1973-9087.22.07136-2. Epub 2022 Apr 12. PMID: 35412036; PMCID: PMC9980509.

(45) Hyman N, Barnes M, Bhakta B, Cozens A, Bakheit M, Kreczy-Kleedorfer B, Poewe W, Wissel J, Bain P, Glickman S, Sayer A, Richardson A, Dott C. Botulinum toxin (Dysport) treatment of hip adductor spasticity in multiple sclerosis: a prospective, randomised, double blind, placebo controlled, dose ranging study. J Neurol Neurosurg Psychiatry. 2000 Jun;68(6):707-12. doi: 10.1136/jnnp.68.6.707. PMID: 10811692; PMCID: PMC1736956.

(46) Middel B, Kuipers-Upmeijer H, Bouma J, Staal M, Oenema D, Postma T, Terpstra S, Stewart R. Effect of intrathecal baclofen delivered by an implanted programmable pump on health related quality of life in patients with severe spasticity. J Neurol Neurosurg Psychiatry. 1997 Aug;63(2):204-9. doi: 10.1136/jnnp.63.2.204. PMID: 9285459; PMCID: PMC2169658.

(47) Penn RD, Savoy SM, Corcos D, Latash M, Gottlieb G, Parke B, Kroin JS. Intrathecal baclofen for severe spinal spasticity. N Engl J Med. 1989 Jun 8;320(23):1517-21. doi: 10.1056/NEJM198906083202303. PMID: 2657424.

(48) Fernández Ó, Costa-Frossard L, Martínez-Ginés M, Montero P, Prieto JM, Ramió L. The Broad Concept of "Spasticity-Plus Syndrome" in Multiple Sclerosis: A Possible New Concept in the Management of Multiple Sclerosis Symptoms. Front Neurol. 2020 Mar 17;11:152. doi: 10.3389/fneur.2020.00152. PMID: 32256440; PMCID: PMC7090019.

(49) Bouafia A, Golmard JL, Thuries V, Sazdovitch V, Hauw JJ, Fontaine B, Seilhean D. Axonal expression of sodium channels and neuropathology of the plaques in multiple sclerosis. Neuropathol Appl Neurobiol. 2014 Aug;40(5):579-90. doi: 10.1111/nan.12059. PMID: 23659577.

(50) Hauser SL, Cree BAC. Treatment of Multiple Sclerosis: A Review. Am J Med. 2020 Dec;133(12):1380-1390.e2. doi: 10.1016/j.amjmed.2020.05.049. Epub 2020 Jul 17. PMID: 32682869; PMCID: PMC7704606.

(51) Ransohoff, R., Hafler, D. & Lucchinetti, C. Multiple sclerosis—a quiet revolution. *Nat Rev Neurol* 11, 134–142 (2015).

(52) Simon O, Yelnik AP. Managing spasticity with drugs. Eur J Phys Rehabil Med. 2010 Sep;46(3):401-10. PMID: 20927006.

(53) Halabchi F, Alizadeh Z, Sahraian MA, Abolhasani M. Exercise prescription for patients with multiple sclerosis; potential benefits and practical recommendations. BMC Neurol. 2017 Sep 16;17(1):185. doi: 10.1186/s12883-017-0960-9. PMID: 28915856; PMCID: PMC5602953.

(54) Yamout BI, Alroughani R. Multiple Sclerosis. Semin Neurol. 2018 Apr;38(2):212-225. doi: 10.1055/s-0038-1649502. Epub 2018 May 23. PMID: 29791948.

(55) AUTHOR=Fernandez Oscar , Costa-Frossard Lucienne , Martínez-Ginés Maria Luisa , Montero Paloma , Prieto-González Jose María , Ramió-Torrentà Lluís TITLE=Integrated Management of Multiple Sclerosis Spasticity and Associated Symptoms Using the Spasticity-Plus Syndrome Concept: Results of a Structured Specialists' Discussion Using the Workmat® Methodology, JOURNAL=Frontiers in Neurology,VOLUME=12, YEAR=2021,URL=https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2021.722801

(56) https://multiplesclerosisnewstoday.com/neurontin-gabapentin-for-pain-management-in-msneurontin-gabapentin-for-pain-management-in-ms/

(57) Priebe MM, Sherwood AM, Graves DE, Mueller M, Olson WH. Effectiveness of gabapentin in controlling spasticity: a quantitative study. Spinal Cord. 1997 Mar;35(3):171-5. doi: 10.1038/sj.sc.3100366. PMID: 9076868.

10. Annexes

Annex 4

(checked during submission process)

Vilniaus universiteto studijuojančiojo, baigiamąjį darbą, GARANTIJA

WARRANTY teikiančio of Vilnius University Student. THESIS

Vardas, pavarde **Surname ,Name:** Stefanie, Tanja Reutter
Padalinys: **Faculty:** Medical Faculty Vilnius
Studijų programa: **Study programm: M**edicine
Darbo pavadinimas: **Thesis topic:**MS spasticity- medical treatment options
Darbo tipas: **Thesis type: S**ystematic Review

Garantuoju, kad mano baigiamasis darbas yra parengtas sąžiningai ir savarankiškai, kitų asmenų indėlio į parengtą darbą nėra. Jokių neteisėtų mokėjimų už šį darbą niekam nesu mokėjęs. Šiame darbe tiesiogiai ar netiesiogiai panaudotos kitų šaltinių citatos yra pažymėtos literatūros nuorodose.
in literature referenc

I guarantee that my thesis is prepared in good faith and independently, there is no contribution to this work from other individuals. I have not made any illegal payments related to this work. Quotes from other sources used in this thesis, directly or indirectly, are indicated

Aš, [Vardas Pavardė], patvirtinu (pažymėti)

I, Stefanie, Tanja Reutter confirm (check) ☐

Patvirtinu, kad baigiamasis darbas yra pateiktas į Vilniaus universiteto studijų informacinę sistemą. I de*clare that this thesis is submitted to the Vilnius University Study Information System.*

_____

(vardas, pavardė / n*ame, surname)* (parašas / si*gnature)* (data / da

Embargo laikotarpis / Embargo period

Prašau nustatyti šiam baigiamajam darbui toliau nurodytos trukmės embargo lai

I am requesting an embargo of this thesis for the period indicated below:

☐ _____ mėnesių/ mo*nths [embargo laikotarpis negali viršyti 60 mėn. / an emb*

☐ embargo laikotarpis nereikalingas/ *no embargo requested.*

Embargo laikotarpio nustatymo priežastis/ r*eason for embargo period:*

…… *……*_____
_____

(vardas, pavardė / n*ame, surname)* (parašas / si*gnature)* (data / da*te).*

Katedros (Padalinio) patvirtinimas, kad atspausdintas baigiamasis darbas buvo pateiktas ir užregistruotas:

_____

(vardas, pavardė) (parašas)
(data)