Pharmacological treatment of patients with MS

A retrospective study with focus on treatment with AEDs and polytherapy with other CNS active drugs

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Master thesis in Pharmacy
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2013

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February 2013

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http://www.duo.uio.no/

Trykk: Reprosentralen, Universitetet i Oslo

Acknowledgements

I would like to express my special thanks to my supervisor Cecilie Johannessen Landmark. I am truly grateful for her guidance and knowledge, without which this project would not have been possible.

I am also very thankful for everything my mother has taught me, and her involvement in this project. I am very proud to have taken part in a scientific study with her.

My gratitude is also extended to Cecilie for her academic assistance and keen eye for details.

Last, but not least I would like to thank Nelli for proofreading my thesis and Silje Andrea for her valued insights.

Abstract

MS patients are often suffering from chronic pain. Pain is a debilitating symptom and treatment is associated with undesirable adverse reactions, especially long-term treatment where tolerance and dependence issues are concerning. Therefore, antiepileptic drugs are frequently being used in the management of chronic pain. Antiepileptic drugs are among the most susceptible drugs to be involved in pharmacokinetic as well as pharmacodynamic interactions. MS patients often use several different types of CNS-active drugs, yet little research has been done to highlight potential polypharmacy issues.

The aim of this study was to investigate the pharmacological treatment of MS patients at the rehabilitation centre for MS, Hakadal, Norway, with regards to current knowledge on polypharmacy, with particular focus on antiepileptic drugs. Medical records from 2009 to 2011 were reviewed and an overview of drug dosages and combinations used by patients at MSSH was created.

The present study demonstrated that one third of MS patients used either an AED (antiepileptic drug) or TCA (tricyclic antidepressant) and that one fifth used two or more. There was no difference in age, gender or degree of disability of the patients using these drugs. Polytherapy was widespread, with up to 19 concomitant drugs in use. Although the AEDs are well-known for their pharmacokinetic interactions, this is not of particular concern for MS patients since they mainly used newer AEDs (pregabalin and gabapentin) with little propensity to interact. Pharmacodynamic interactions are of greater concern since more than half of the patients used an opioid, a benzodiazepine or baclofen in addition to their AED/TCA therapy. One third of the patients were elderly and careful considerations regarding pharmacokinetics and possible excessive adverse reactions are of importance. More focus on individualisation of treatment by implementation of therapeutic drug monitoring of AEDs and TCAs and attention to potential pharmacodynamics interactions may be further treatment concerns.

List of abbreviations

AED	antiepileptic drug
CYP	cytochrome P450
GBP	gabapentin
EDSS	expanded disability status score
MAO	monoamine oxidase
MRI	magnetic resonance image
MSSH	MS-senteret Hakadal
NNT	number–needed–to–treat
PGB	pregabalin
PML	progressive multifocal leukoencephalopathy
PPMS	primary progressive multiple sclerosis
RRMS	relapsing–remitting multiple sclerosis
s.e.	standard error
SNRI	selective noradrenaline reuptake inhibitor
SmPC	summary of product characteristics
SPMS	secondary progressive multiple sclerosis
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TDM	therapeutic drug monitoring

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1. Introduction

1.1 Background

Multiple Sclerosis (MS) is an inflammatory, neurodegenerative disease of the central nervous system. Prevalence varies throughout the world and Norway has a high prevalence of about 150 per 100,000 (Torkildsen et al. 2007).

MS treatment has received considerable attention in Norwegian press lately due to the high costs of newly approved drugs and even more expensive experimental treatment options (Bakke 2012). Treating a single patient with currently available disease-modifying drugs costs at least 200,000 NOK per year. An economic report on MS costs estimated a yearly cost to the Norwegian society of € 65,000 (≈477,000 NOK) per patient and a total of € 439 million (≈3,222 million NOK) for the entire Norwegian MS population (Svendsen et al. 2012). This fact, combined with the unsatisfactory nature of current MS treatment, displays the vast potential for improvement of treatment, both disease-modifying and symptomatic.

MS patients are often suffering from chronic pain. Pain is a debilitating symptom and treatment is associated with undesirable adverse reactions, especially long-term treatment where tolerance and dependence issues are concerning. Therefore, antiepileptic drugs are frequently being used in the management of chronic pain. Antiepileptic drugs are among the most susceptible drugs to be involved in pharmacokinetic as well as pharmacodynamic interactions (Johannessen Landmark and Patsalos 2010). It is probable that MS patients use several different types of CNS active drugs, yet little research has been done to highlight potential polypharmacy issues.

1.1.1 Centre for MS-Rehabilitation Hakadal, Norway – MSSH

The centre is a tertiary centre founded in 1976 and a part of the sector for specialised healthcare in Norway. It is owned by the National Norwegian MS organisation and run as an independent non-profit business. Patient stays are funded by Norwegian health authorities. MSSH's main goal is to be a professional resource centre and a key cooperative for health regions and personnel concerning MS treatment (mssh.no).

1.1.2 Aim of the study

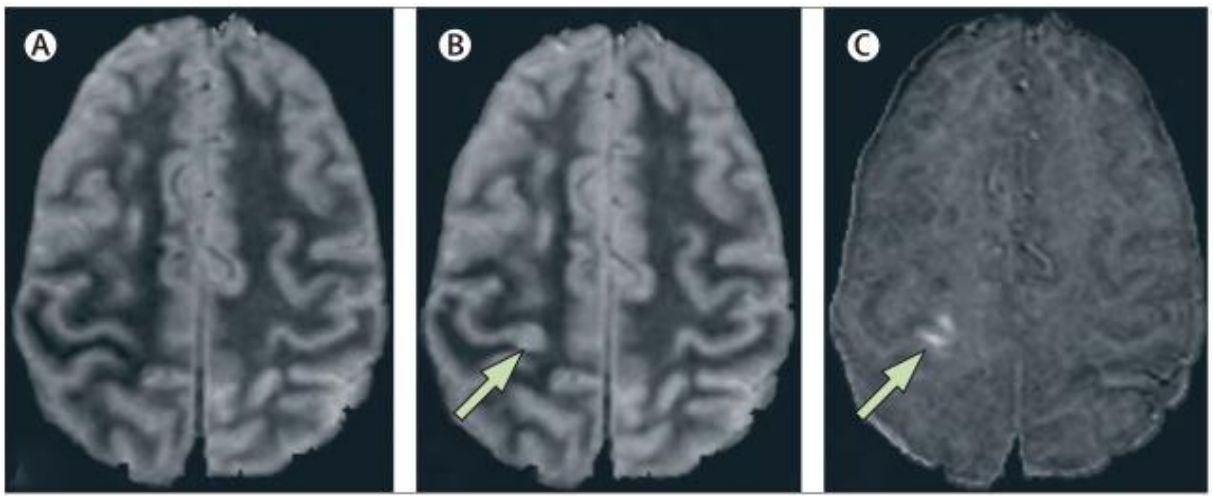
The aim of this study is to investigate the pharmacological treatment of MS patients at MSSH with regards to current knowledge on polypharmacy, with particular focus on antiepileptic drugs. It is therefore necessary to record and create an overview of drug dosages and combinations used by patients at MSSH. By comparing these results with recent international guidelines on treatment of neuropathic pain by antidepressants and antiepileptic drugs, we hope to reveal a potential for improvement in the pharmacological treatment of pain in MS patients.

1.2 Multiple Sclerosis

1.2.1 Diagnosis

Multiple Sclerosis is an inflammatory autoimmune disease of the central nervous system. The disease was first defined by the French neurologist Jean-Martin Charcot in 1868. Charcot related plaques, areas of damaged myelin in the central nervous system, found during autopsies to their clinical manifestations (Clanet 2008). When diagnosing patients, Charcot had to rely solely on clinical findings. These days, the diagnosis of MS is usually made after both clinical and laboratory findings, including the use of an MRI (magnetic resonance imaging) scan. An MRI scan enhances the inflammation around the blood vessels caused by active lesions following a gadolinium injection, partly due to leakage of the blood−brain barrier. Schumacker et al. defined two criteria for MS diagnosis in 1965, dissemination in time (DIT) and space (DIS) (Schumacker et al. 1965). Other possible diseases must also be eliminated before a definite MS diagnosis can be made. For example, in Norway and other countries with a known risk of tick bites, the cerebrospinal fluid should be tested to exclude Lyme's disease. Dissemination in time refers to CNS lesions at different times, and dissemination in space means CNS lesions in different places in the nervous system. Clinically fulfilling these criteria requires at least two attacks (DIT) with different symptoms representing lesions at different places in the nervous system. If only one attack has been described clinically, an MRI scan at a later time can display a lesion at a different place, establishing DIT and DIS, without clinical manifestations of this second attack. An MRI scan of a new lesion after a three year follow-up is shown in figure 1. These criteria are still the mainstay for MS diagnosis. For further details on current MS diagnosis criteria, the

reader is referred to the latest review of the internationally established McDonald criteria published by the American Neurology Association (Polman et al. 2011).



(Bakshi et al. 2008)

Figure 1. New juxtacortical lesion of 44–year–old–woman. A: Baseline; B: New lesion 3 years later; C: Subtract image of A and B diplays lesion clearly

1.2.2 Epidemiology

MS has a mean age of onset at about 30 years (Weinshenker et al. 1989). More women are affected than men (Duquette et al. 1992). Prevalence varies throughout the world with 2 million patients affected globally, and northern Europe and America have the highest rates (Koch-Henriksen and Sorensen 2011). Norway has a high prevalence of about 150 per 100,000 (Torkildsen et al. 2007). The incidence in Norway is about 300 new patient cases per year (Smestad et al. 2008).

1.2.3 Pathophysiology

MS comes in several forms, with distinct characteristics and prognosis representing variations in the underlying pathoetiology and pathophysiology. The most common division is based upon the status of disease progression, comprising three different groups (displayed in figure 2): Relapsing–Remitting MS (RRMS), Primary Progressive MS (PPMS) and Secondary Progressive MS (SPMS). MS patients are also divided by their age at disease onset, the typical groups are: early-onset MS (younger than 16; EOMS), adult-onset MS (between 16 and 50; AOMS) and late-onset MS (after 50; LOMS). Only 3 % of patients have an EOMS (Duquette et al. 1987) and 6 % have a LOMS (Weinshenker et al. 1989).

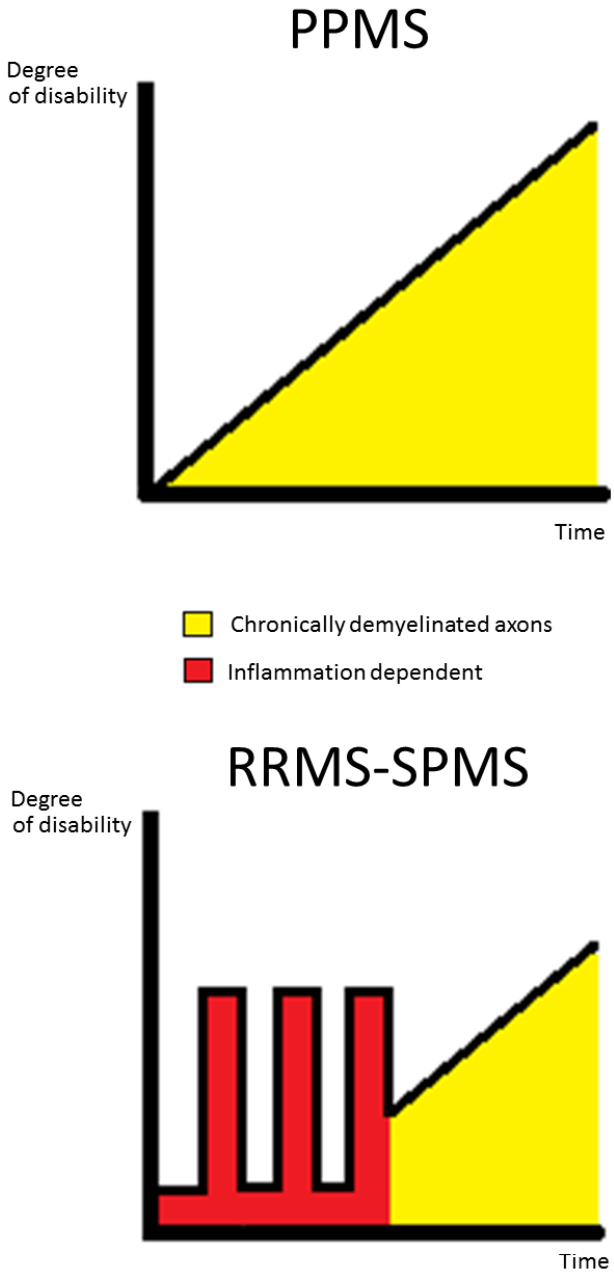


Figure 2. Disease-course of MS. PPMS (Primary Progressive MS); RRMS (Relapsing–Remitting MS); SPMS (Secondary Progressive MS)

1.2.4 Relapsing–Remitting MS

Approximately 85 % of MS patients initially have RRMS (Trapp and Nave 2008). RRMS is well-known for periods of alternating neurological disability and recovery. RRMS patients develop new, active "MS lesions". Active lesions are lesions with active inflammation, which cause reversible oedema blocking the conduction of action potentials. This, in addition to demyelination throughout the CNS is a major contributor to temporary loss of function in

RRMS patients. There are a number of mechanisms activated to restore function to demyelinated axons. For example, redistribution of voltage-gated sodium channels along the demyelinated axolemma (Waxman 2006, Dutta and Trapp 2011). This restores action potential conduction in the axon at a reduced velocity. Finally, the axon is remyelinated after the oedema has resolved.

Progressive axonal loss is the major cause of permanent neurological disability in MS. After immune-mediated breakdown of myelin the axon is vulnerable to the destructive processes of inflammation. Processes causing axonal transection are thought to include accumulation of amyloid precursor proteins, phosphorylation of axonal neurofilaments, glutamate-mediated excitotoxicity and release of proteolytic enzymes, matrix metalloproteases, cytokines, oxidative products and free radicals by activated immune and glial cells (Dutta and Trapp 2011). Significant axonal loss has been seen in RRMS patients with short disease duration without permanent disabilities, displaying the fact that the brain has an ability to compensate for neuronal loss. It seems that a certain threshold of axonal loss must be reached before there are any clinical manifestations. RRMS patients develop SPMS once the brain no longer can compensate for neuronal loss (Nave and Trapp 2008).

1.2.5 Primary and Secondary Progressive MS

About 10 % of MS patients have a disease-course characterised by steady neurological deterioration without recovery, classified as PPMS. PPMS is associated with older age at onset than RRMS (Myhr et al. 2001). Most patients (90 %) with initial RRMS will, after 25 years, experience the same steady decline in function without recovery, this is termed SPMS (Dutta and Trapp 2011). In contrast to RRMS patients, SPMS patients decline in function without signs of new lesions. The well-established explanation for this decline in function is a progressive loss of chronically demyelinated axons. PP/SPMS patients do not respond to immunomodulatory treatment in contrast to RRMS patients, supporting the theory of chronically demyelinated axons in PP/SPMS.

1.2.6 Expanded Disability Status Scale – EDSS

In 1983 John F. Kurtzke published the Expanded Disability Status Scale for evaluating the disability of MS patients (Kurtzke 1983). The EDSS is still the most commonly used tool for

numerically describing the disability status of MS patients in both treatment and natural history studies. To determine the EDSS score of a patient, a thorough neurological examination is required. The EDSS has been tested and validated internationally (Kurtzke 2008). Please see appendix 6.1 for further details.

1.2.7 Symptoms and comorbid disorders

There is a fine line between symptoms and comorbid disorders in complicated autoimmune diseases such as MS, they can be overlapping and classification may be a matter of debate. Therefore, they are presented together without further discussion.

Neuropathic pain

Neuropathic pain was in 2011 defined by the International Association for the Study of Pain (IASP) as "pain caused by a lesion or disease of the somatosensory system" (Jensen et al. 2011). Neuropathic pain is unrelated to any peripheral tissue injury. The pathophysiological mechanisms are poorly understood. Spontaneous firing of voltage-gated sodium channels, due to improper regulation and overexpression caused by release of hyperalgesic pro-inflammatory agents is thought to play a role (Chahine et al. 2005). Damaged sensory neurons can express α-adrenoceptors, thus responding to physiological sympathetic stimuli, which they normally would not. This phenomenon is described as sympathetically mediated pain (Rang et al. 2007).

Neuropathic pain may be of central or peripheral origin. In multiple sclerosis, central neuropathic pain is defined as present if there is a central nervous system lesion regionally consistent with the pain distribution, but both nociceptive and peripheral neuropathic pain must be excluded (Osterberg et al. 2005). In a study of 364 MS patients, Osterberg et al. reported that 57.5 % had suffered from pain during their disease-course; 27.5 % suffered from central pain, 21 % from nociceptive, 2 % from peripheral neuropathic pain and 1 % was related to spasticity.

Although pharmacological treatment of neuropathic pain is efficacious in most patients, complete pain-relief is difficult to achieve. Drugs commonly used have similar efficacy across the spectre of diseases causing neuropathic pain, except for trigeminus neuralgia,

radiculopathy and HIV neuropathy (Attal et al. 2010). Central pain, including trigeminus neuralgia, is most commonly experienced by MS patients. Currently available drugs for treating central pain include tricyclic antidepressants (TCA), antiepileptic drugs (AED), selective noradrenalin reuptake inhibitors (SNRI), cannabinoids and opioids. The European Federation of Neurological Societies (EFNS) guideline recommends carbamazepine as first-line treatment for trigeminal neuralgia and amitriptyline, pregabalin or gabapentin for central pain (Attal et al. 2010). The mechanisms of action and documentation on the use of the different drugs will be reviewed in more detail in section "1.3.3 Symptomatic treatment".

Epilepsy

Epilepsy is defined as a neurological disorder and it is one of the most common ones worldwide; the global prevalence is 0.7 to 1 % (Elger and Schmidt 2008). An increased risk of developing epilepsy is related to several neurological diseases and syndromes. Koch et al. found 30 different studies with more than 50 patients which studied the epilepsy prevalence in different MS populations. The epilepsy prevalence varied between 0.6 and 8 %. In their review they pooled all the studies with a total of 19,804 MS patients and the frequency of epileptic seizures was estimated as 2.2 % (Koch et al. 2008). The prevalence of epilepsy in the general population is between 0.5 and 1 % (Sander 2003, Elger and Schmidt 2008). Increased risk of epilepsy in MS patients is widely accepted as true, the explanation for this, is, however, still not fully understood.

Narcolepsy

Sleep disorders are common among MS patients, prevalence estimates vary between 25 and 54 % (Brass et al. 2010). Narcolepsy is particularly interesting, as it shares genetic risk factors with MS. Nearly all patients suffering from narcolepsy (95 %) and 50–60 % of MS patients express the DR2 haplotype (Caminero and Bartolome 2011). The narcolepsy prevalence in the general population in Europe is 3–5 for every 10,000 individuals. In a study of 116 patients with narcolepsy, MS was the fourth most common cause (n=10) (Nishino and Kanbayashi 2005). The fact that fatigue is so common among MS patients makes narcolepsy an important differential diagnosis for the physician to keep in mind.

Other symptoms and disorders

Migraine, inflammatory bowel disease, irritable bowel syndrome, chronic lung disease and secondary osteoporosis have also been reported as more common among MS patients than the general population. Common MS symptoms beyond the scope of this thesis include spasms, fatigue, cognitive issues, depression and anxiety (Beiske 2009).

1.3 Treatment of MS

The different treatment options for MS are summarised in table 1.

Table 1. Treatment of MS

Treatment of MS	Rationale	Examples
Attacks (RRMS only)	Reduce impact of the attack	methylprednisolone
Disease-modifying (RRMS only)	Reduce number of attacks and possibly slow progression of disability	1st line: Beta-interferons and glatiramer acetate 2nd line: Natalizumab and fingolimod 3rd line: mitoxantrone

Symptomatic treatment is at least as important as disease-modifying treatment to reduce disease-burden and improve quality of life. Symptomatic treatment applies to all patients, regardless of their disease-course classification. Common treatment options for MS symptoms are listed in table 2.

Table 2. Symptomatic treatment options

Symptomatic treatment	Drug class	Examples
Anxiety	Benzodiazepine	Diazepam
Spasms	Antispasmodic	Baclofen, botulinum toxin
	Benzodiazepine	Clonazepam
	AED	Pregabalin, gabapentin
Depression	SSRI	Escitalopram, paroxetine
	SNRI	Venlafaxine
	TCA	Imipramine
Insomnia	Z-hypnotic	Zopiclone, zolpidem
Bladder dysfunction	Muscarinic antagonists	Solifenacin, tolterodine
Migraine	Triptan	Sumatriptan, rizatriptan
	Ergot alkaloid	Ergotamine
Neuropathic pain	AED	Gabapentin, pregabalin
	Opioid	Tramadol, oxycodone
	TCA	Amitriptyline
General pain	Mild analgesic	Paracetamol, ibuprofen
	Opioid	Tramadol, codeine

1.3.1 Treatment of attacks

As described above, RRMS patients have periods of temporary neurological deterioration; these periods are commonly known as "attacks". The attacks are caused by inflammation as a result of active lesions. The national guideline for MS treatment dictates that attacks with clinically significant decline in function should be treated with anti-inflammatory medications such as methylprednisolone. Possible infections must be ruled out and treatment should commence as soon as possible, preferably within one to two weeks (Myhr et al. 2010).

1.3.2 Disease-modifying treatment

Currently available disease-modifying drugs are only useful for treatment of RRMS. There are several available treatment options in Norway, divided in to three categories: first-, second- and third-line treatment. First-line treatment options are beta-interferons and

glatiramer acetate. These drugs have been used since the 1990s. Although they reduce attacks by about 30 %, any effect on permanent invalidity seems to be rather limited (Holmoy and Celius 2011). Flu-like symptoms and adverse reactions related to injection are common, since the drugs have to be injected on either a daily or weekly basis. Interferons have been shown to inhibit cytochrome P450 (CYP) enzyme activity, particularly interferon-alpha in treatment of patients with hepatitis C (Christensen and Hermann 2012). Previously interferon-alpha was also used in treatment of RRMS. Interferon-beta has not yet been shown to affect CYP metabolism in MS patients.

The second-line treatment options are natalizumab and fingolimod. They cost twice as much as the first-line alternatives, approximately € 25,000 (≈200,000 NOK) per patient per year. Natalizumab is a monoclonal antibody administered at the hospital by monthly infusions. Fingolimod (sphingosine 1-phosphate receptor modulator) is available in tablets for daily administration. Natalizumab binds α-integrin-4, thereby blocking it from binding to its ligand. The net result is blockage of the peripherally activated immune cells' migration across the blood–brain barrier. Natalizumab can cause a very rare and dangerous adverse reaction, progressive multifocal leukoencephalopathy (PML). The second-line treatments are approved for use in patients with active disease, after failing first-line treatment or for patients with a particularly rapid and debilitating disease-course (Myhr et al. 2010).

Third-line treatment in Norway is chemotherapy (mitoxantrone). Only few patients currently receive this treatment, due to cardiotoxicity and risk of developing leukaemia.

1.3.3 Symptomatic treatment

MS patients suffer from a wide range of symptoms. Some symptoms are often treated efficaciously including pain, paroxysmal symptoms, spasticity, depression, bladder and sexual dysfunction. Other MS symptoms such as fatigue, cognitive dysfunction, ataxia, dysarthria, dysphagia, bowel dysfunction, visual loss and oculomotor symptoms lack evidence-based treatment options (Beiske 2009). Drugs with central effects often used for treatment of MS patients are especially relevant to this thesis and will be discussed in more detail below. An overview of pharmacological targets for relieving central pain is given in figure 3.

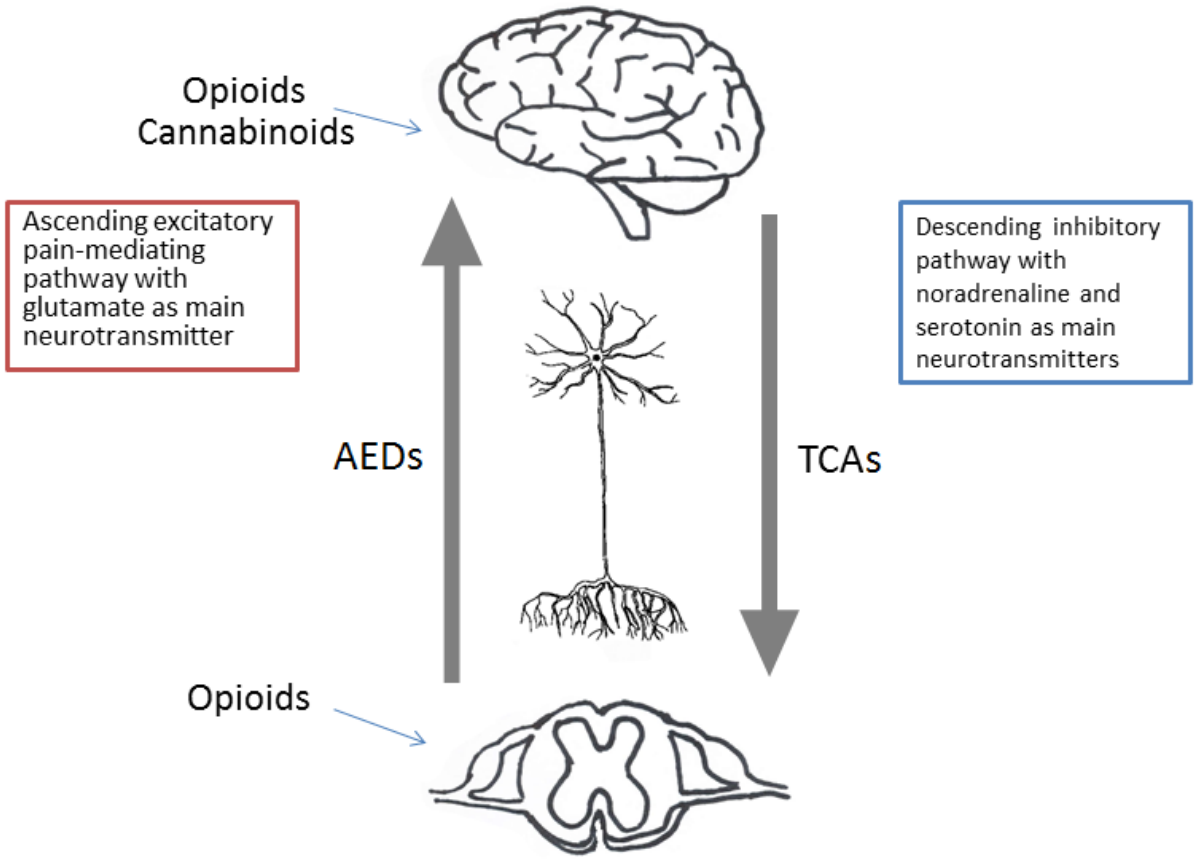


Figure 3. Pharmacological targets for relieving central pain (AED: antiepileptic drug; TCA: tricyclic antidepressant)

Antidepressants

The mainstay of pharmacological treatment of depression is in accordance with the monoamine hypothesis proposed by Schildkraut in 1965 (Rang et al. 2007). Antidepressant drugs fall in to one of the three following categories, inhibitors of monoamine uptake (TCAs, SSRIs and SNRIs), monoamine oxidase inhibitors (reversible MAO-A selective and irreversible unselective inhibitors) or atypical receptor-blocking agents (St. John's wort, mianserin etc.) (Licinio and Wong 2005). The mechanisms of action of drugs in the latter category are poorly understood. It takes at least two weeks before any antidepressant effects are seen, even though the drugs immediately exhibit their effects on the receptors.

Interestingly, the TCAs have also been proven efficacious in treatment of neuropathic pain. A recent Cochrane review on the use of antidepressants in the treatment of neuropathic states that amitriptyline exhibits the best documented effect on neuropathic pain. Furthermore its NNT (number–needed–to–treat) was calculated to 3.1 (95 % CI 2.5 to 4.2) (Saarto and Wiffen

2007). The specific mechanism for TCAs' pain relieving effect has remained elusive, however, β_2-adrenoceptors have been shown to play a critical role (Yalcin et al. 2009).

Antispasmodics

First-line treatment of spasms is with baclofen. Baclofen is a GABA agonist, designed as a lipophilic derivative of GABA to enhance its transport across the blood–brain barrier. Selectively binding at pre-synaptic $GABA_B$ receptors, it inhibits both mono- and polysynaptic activation of motor neurons in the spinal cord (Rang et al. 2007). Adverse reactions include drowsiness, motor incoordination and nausea. Severe spasticity is sometimes treated with a programmable intrathecal baclofen pump.

Botulinum toxin is a neurotoxin causing long lasting paralysis and is used to treat spasms in specific muscles. Botulinum toxin exhibits its effect by inhibiting acetylcholine release. Systemic adverse reactions are avoided, because it is injected peripherally.

Recently the cannabinoid oromucosal mouth spray "Sativex" has been approved for use in MS patients with unsatisfactory effect from first-line antispasmodic treatment (Hortemo 2012). It is, however classified as an analgesic and antipyretic drug, according to the ATC register (whocc.no). It has proven efficacious for treatment of spasms in randomized placebo-controlled trials (Oreja-Guevara 2012). Sativex has also been studied with regards to its effect on central pain in MS patients, the effect was significant, however the adverse reactions should still be investigated further (Chaparro et al. 2012, Langford et al. 2012).

Clonazepam can also be used to treat spasms. It is often administered in the evening, due to its sedative effect.

Antiepileptic drugs

There are three main mechanisms of action for antiepileptic drugs, enhancement of GABAergic action, inhibition of glutamatergic excitation and inhibition of voltage-gated sodium and calcium channels. The first known class of antiepileptic drugs, benzodiazepines, act by allosterically modulating the $GABA_A$ receptor, thus enhancing its time spent in the active confirmation and thereby increasing Cl^- conductance.

Carbamazepine inhibits voltage-gated sodium channel function with a higher affinity for the inactivated state of the channel. Since there are more inactivated channels in a neuron firing repetitively, these drugs preferentially block the excitation of neurons that are firing excessively (Perucca 2005). A major reason for discontinuation of carbamazepine treatment both in epilepsy and MS patients is skin rash (Shirzadi et al. 2012).

Gabapentin was designed to resemble GABA, but also, unlike GABA, cross the blood−brain barrier. The idea was for gabapentin to bind GABA receptors and thereby mimic its effects. Although gabapentin did reduce seizures in animal models, it did not bind to GABA receptors. Instead, it was found to block L-type calcium channels by binding specifically to the $\alpha_2\delta_1$-subunit (Sills 2006). The L-type calcium channel is voltage-gated and mediates long lasting potentials. Gabapentin has been shown to affect several physiological targets, it seems however, that the inhibition of the voltage-gated calcium channel is predominantly responsible for its pharmacological actions (Sills 2006).

In addition to its anticonvulsant effect, gabapentin has also shown efficacy in treatment of neuropathic pain. Several potential mechanisms for gabapentin's effect on neuropathic pain have been proposed and one does not exclude the other. Gabapentin's antinociceptive action may result from direct inhibition of the afferent signal to the spinal cord, and also it has been shown to reduce the enhanced spinal glutamate release following noxious stimuli in neuropathic rats (Johannessen Landmark 2008). It is believed that binding to the $\alpha_2\delta_1$-subunit of calcium channels is responsible for gabapentin and pregabalin's pain-relieving effect (Johannessen Landmark 2008). Pregabalin is a more potent follow-up of gabapentin with similar pharmacological actions. These two drugs are predominantly utilised in treatment of neuropathic pain (Johannessen Landmark et al. 2009).

Benzodiazepines

The first benzodiazepine, chlordiazepoxide, was synthesised in 1961. Today, benzodiazepines are used for their anxiolytic, hypnotic and anticonvulsant effects. Benzodiazepines act selectively on $GABA_A$ receptors, allosterically increasing the affinity of GABA for the receptor. The unwanted effects vary with indication and between specific substances; their joint flaw in long-term treatment is the development of dependence and tolerance. The newer generation of benzodiazepines used to treat insomnia, termed Z-hypnotics (e.g. zopiclone,

zolpidem), have a shorter half-life (1–6 hours) and cause less of a hangover than their predecessors (Mellingsaeter et al. 2006).

Opioids

The well-known powder, opium, has been used for thousands of years, both medicinally and socially. Opium consists of a number of alkaloids related to morphine. Opiates are structures resembling morphine, whereas opioids are all substances producing morphine-like effects that can be blocked by an antagonist (e.g. naloxone).

Opioids are the most effective analgesics available, unfortunately inseparable from tolerance and dependence issues (Plante and VanItallie 2010). There are mainly three different opioid receptors, μ, δ and κ. The endogenous ligands are termed enkephalins (peptides). Different substances have different binding profiles with regard to the receptor subtypes. The binding profile of any given substance determines its *in vivo* effects (Plante and VanItallie 2010). The μ-receptor is responsible for most opioid effects, including physical dependence.

Codeine is a pro-drug for morphine and other active metabolites. Codeine is more reliably absorbed when administered orally than morphine. Codeine only has 20 % of the analgesic effect of morphine and it does not increase much at higher doses. The risk of abuse and dependency is little and therefore it is sold without prescription in some countries (Rang et al. 2007). About 10 % of the population lacks the enzyme converting codeine to morphine and will therefore, not experience any effects.

1.3.4 Drug interactions

The many symptomatic and fewer disease-modifying treatment options available, often result in polypharmaceutic treatment of the individual patient. Therefore, awareness of potential interactions is of major importance. Age and gender may have an impact on the likelihood of interaction development (Gidal et al. 2009). The clinical consequence of a specific drug interaction may be anything from irrelevant to fatal. Different aspects of the pharmacological treatment may be affected, such as the drug efficacy or the adverse reaction profile.

Drug interactions are either pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions affect drug absorption, distribution, metabolism and/or excretion. They are often

the result of limited capacity of endogenous enzymes in intestine, liver or kidneys. Pharmacokinetic interactions alter the serum drug concentration (Johannessen Landmark and Patsalos 2010). Pharmacodynamic interactions may arise when multiple drugs affect the same target protein, but they do not affect the serum drug concentration. One example could be a synergistic effect, achieved by using two different blood-pressure lowering drugs to sustain a lower blood-pressure than what could be achieved with a higher dosage of a single drug. Several hundred pharmacokinetic interactions involving AEDs have been reported, but only a handful pharmacodynamic interactions (Johannessen Landmark and Patsalos 2010).

1.4 Life with MS

Multiple sclerosis is the most common neurologically debilitating disease among young adults. The many disorders associated with MS combined with the broad spectre of MS symptoms, including cognitive, motoric and sensory symptoms, highlight the need for a wide range of therapeutic approaches by many different professionals to treat the individual patient optimally. Therefore, the staff at MSSH includes eight different professions (e.g. neurologist, neuropsychologist, general psychologist, physiotherapist, occupational therapist, nurses, social workers and a nutritionist) (mssenteret.no 2013).

The median time from disease onset to the patient reaches EDSS level 4.0 (limited walking distance) is 8–10 years and the median time to reach EDSS level 7.0 (need wheelchair) is 30 years (Beiske 2009). Health-related quality of life is lower in MS, than in other chronic disorders. MS patients experiencing pain symptoms have an overall lower quality of life than those without pain (Svendsen et al. 2005). Sustaining employment after the MS diagnosis and a higher level of education is associated with better quality of life (Patti et al. 2007).

2. Material and methods

2.1 Study material

The study was performed at the Centre for MS-rehabilitation Hakadal, Norway. The present study is a retrospective study of pharmacological treatment of patients admitted to the MS centre, based on data from the medical records.

All medical records at MSSH are stored in a local administrative database, accessible through designated software named Extensor. To access these records I was given administrative privileges in Extensor and had to sign a confidentiality agreement. All records from the period 01.01.2009 to 31.12.2011 were reviewed, representing a total of 869 unique patients. Information on patients treated with at least one AED or amitriptyline (a tricyclic antidepressant) was collected. This was done to investigate the suspected polypharmacy issues and potential for pharmacokinetic and pharmacodynamic interactions following use of AEDs. Amitriptyline was added as an inclusion criteria, as it is used in treatment of neuropathic pain and could cause pharmacodynamic interactions, in line with AEDs.

2.2 Inclusion criteria

The inclusion criteria were the MS diagnosis and the use of at least one antiepileptic drug or amitriptyline. Antiepileptic agents were defined as any drug with ATC-code N03Axxx, according to the Norwegian ATC-register (Anatomical Therapeutic Chemical classification). All patients registered in the Extensor database are diagnosed with MS. Some patients had more than one stay at the centre during the inclusion period. In those cases the most recent stay was chosen and previous stays were disregarded.

If the medical record included an EDSS score, the EDSS score together with the patient's gender and age was collected, even if the patient failed to meet the inclusion criteria. This was done to provide a means to characterise the total patient population with an EDSS profile and thus evaluate how well it represents the national MS population. An EDSS profile of the study population describes a distribution of functioning scores among the patients. Comparing the study-population's EDSS profile with a regional distribution will show whether the study results may apply to other MS populations as well.

For the inclusion year 2009, all patients receiving disease-modifying treatment were included. This was done to investigate potential interactions, characterise the study population and possibly to contribute in the ongoing debate of financing disease-modifying treatment of MS patients.

2.3 Exclusion criteria

Exclusion criteria were lack of treatment with either an AED or amitriptyline. Patients without stays at the MS centre during the inclusion period (01.01.2009 to 31.12.2011) were also excluded. Medical records with insufficient data regarding gender or age were disregarded.

2.4 Registration and storage of patient data

For every included patient, the following was registered in the spread sheet:

- Age
- Gender
- EDSS score
- Epilepsy diagnosis
- All current medication including dosages
- Extensor patient id number

The Extensor patient id number is a number assigned by Extensor for every new patient stored in the database. Registering this number with every patient in the spread sheet allows tracking for quality assurance aspects and improves patient data safety compared to assigning study-specific patient id numbers and creating a key spread sheet. In this way, only those with access to the original medical records in Extensor are able to identify patient identities from the study's spread sheet.

2.5 Study scope

Some drugs were considered especially relevant for potential interactions (mostly pharmacodynamic) with AEDs and amitriptyline. To study the use of those drugs in more detail, they were divided into subgroups based on their mechanism of action. Potential groups which would have contained less than five patients were disregarded. Data belonging to each of the following groups was studied in separate spread sheets:

Table 3. Drug subgroups

Group name	Examples	
Alpha-2 blockers	Mianserin, mirtazapine	
Antispasmodics	Baclofen	
Benzodiazepines	Z-hypnotics: Zolpidem, zopiclone	Other: Diazepam
Opioids*	A: Oxycodone, buprenorphine	B: Tramadol, codeine
SSRIs and SNRIs	Escitalopram, venlafaxine etc.	
Central stimulants	Modafinil	

*All drugs in Norway are divided into prescription classes depending on their characteristics. Classes "A" and "B" have a potential for abuse and there are special requirements following those prescriptions. With a few important exceptions, opioids are in class "A", which is the class associated with the greatest risk of abuse. The dividing of opioids in classes "A" and "B" seems appropriate, due to the important differences between the opioid substances and henceforth all matters regarding opioids in this thesis will reflect upon this classification.

2.6 Calculations and statistical analysis

The entire studied population included 869 unique patients. However, since some patients failed to meet any of the inclusion criteria, the gender and age of only 566 patients was recorded. EDSS scores were available for 343 patients.

The collected data was filtered and processed using Open Office calc (version 3.3.0). The statistical program Minitab (version 16.1.0) was used for performing statistical tests and creating figures. Microsoft Excel 2010 (version 14.0.) was also used to create figures and tables. P-values ≤ 0.05 were considered as statistically significant. The following statistical

tests were applied: Fischer's t-test for binomial distributions, Mann-Whitney for comparing non-parametric data (EDSS scores) and student's t-test when comparing normally distributed data (for example drug dosages).

2.7 Ethical considerations

The study was approved by the local ethics committee at MSSH. All data were handled anonymously and retrospectively. The study results will benefit the study population. Since the nature of this study is quality assurance of treatment with AEDs at MSSH, it was considered no need for patient informed consent according to Norwegian law (helseforskningsloven). Otherwise, performing such studies would not be possible.

3. Results

3.1 Study population

The included study population and subpopulations from MSSH are schematised in figure 4.

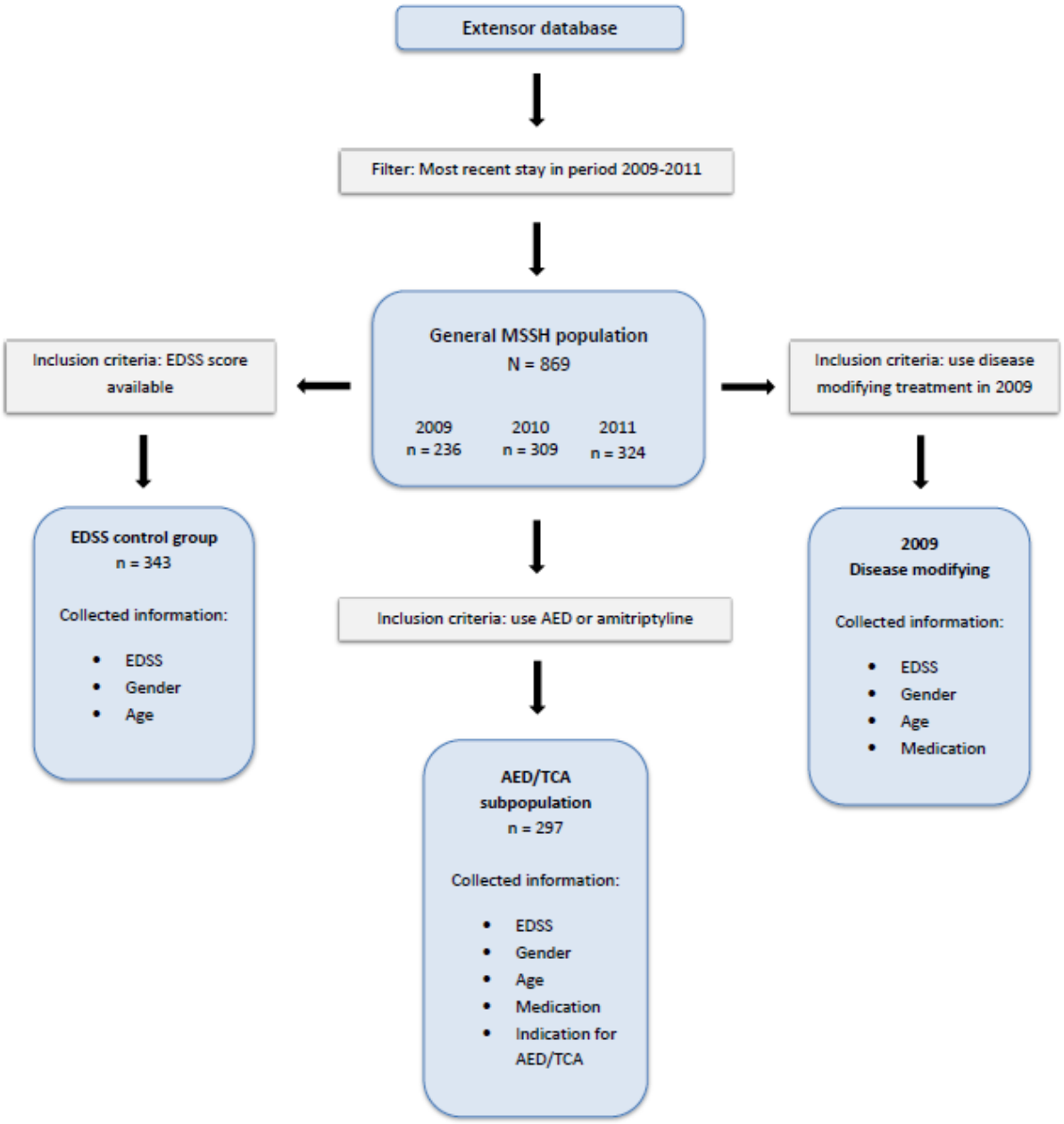


Figure 4. General study population and subpopulations

3.2 Demographics

3.2.1 Demographic characteristics of the general MSSH population

The mean age and EDSS score of all available patient data is displayed in table 4. The mean age was 54 for both genders and their average EDSS scores were consistent. As expected in any unbiased MS population, there were about 70 % women.

Table 4. MSSH demographic

	N	Age: mean (range)	EDSS: mean (range; N*)
Registered population	566	54.4 (20–77)	4.8 (1–8; 343*)
Women	388	54.3 (20–74)	4.7 (1–8; 237*)
Men	178	54.7 (25–77)	4.9 (2–8; 106*)

**Gender and age is included in all medical records, unfortunately some medical records lacked an EDSS score, the number of available EDSS scores in each group is denoted in the last column.*

The age distribution of the registered population is displayed in figure 5. There was a large increase in frequency of men from the 30–39 age group to the 40–49 age group. There is also a large increase in the frequency of women in the age group 50–59 compared to the 40–49 age group.

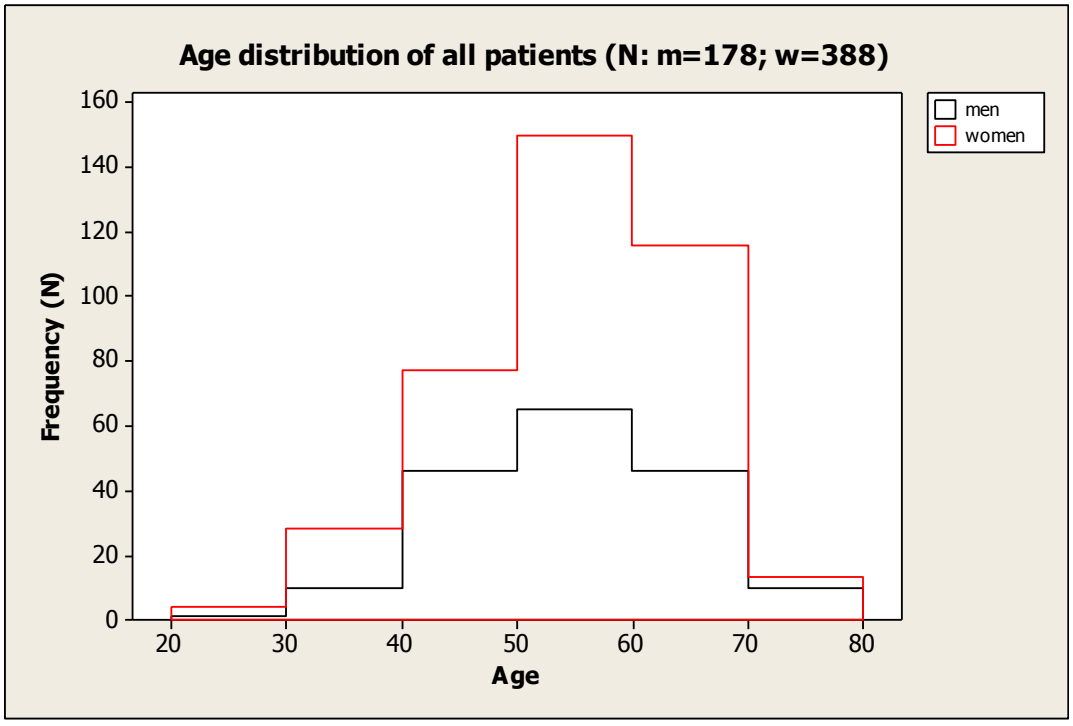


Figure 5. MSSH age distribution

The EDSS score distribution of all available EDSS scores (n=343) from the entire population (n=869), is shown in figure 6.

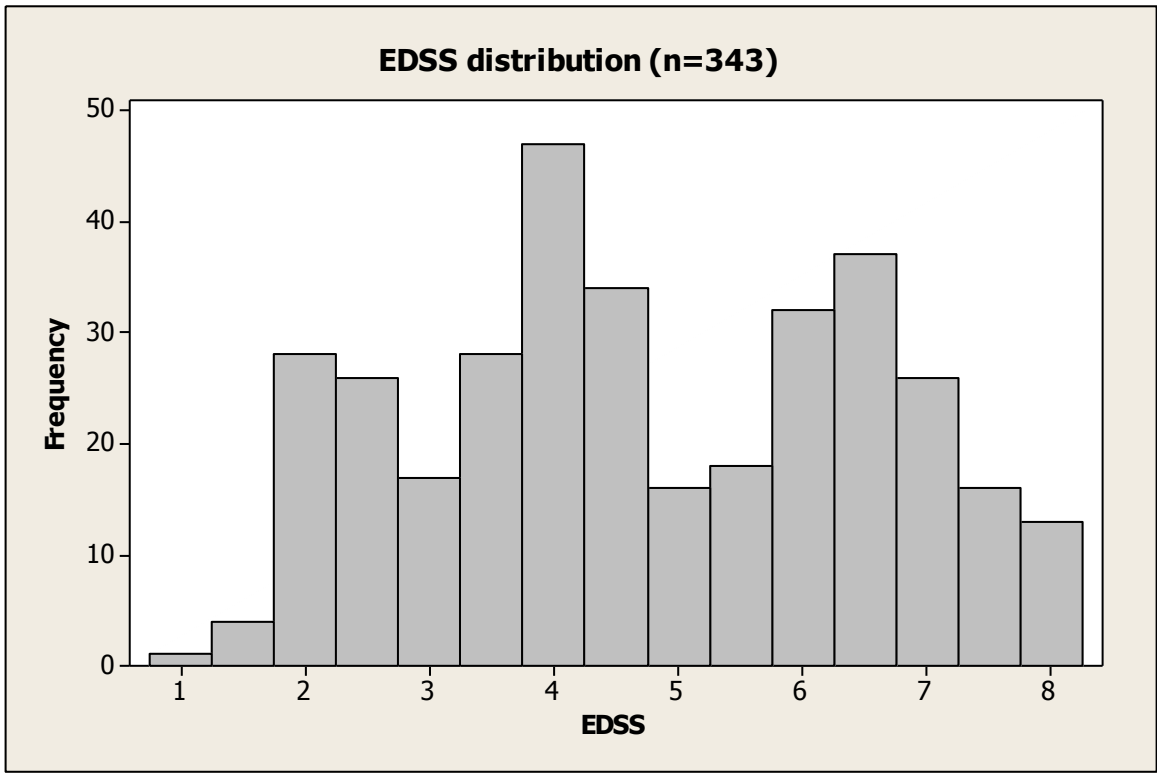


Figure 6. EDSS distribution

3.2.2 Patients using AEDs or TCAs

There were 23 patients with epilepsy in addition to MS, representing 2.6 % of the general MSSH population and 7.7 % of the AED/TCA population. The focus of this study further on is, however, the use of AEDs and TCAs in the treatment of pain.

The mean EDSS score of the AED/TCA population is 4.82 (n=140), whereas the population of non-AED/TCA users has an average EDSS score of 4.72 (n=208). The mean age of the AED/TCA users is 55.2 (n=297) and for the non-users it is 53.4 (n=260). An overview of the AED/TCA demographic and corresponding EDSS scores is given in table 5.

Table 5. AED/TCA demographic

Age	N	Avg EDSS (N)	[Women]
20–29	3	3.5 (2)	67 %
30–39	17	4.2 (3)	82 %
40–49	52	4.7 (30)	67 %
50–59	119	4.7 (65)	70 %
60–69	95	5.6 (36)	71 %
70–79	11	4.25 (4)	73 %

The AED/TCA subpopulation included 106 (35.7 %) patients who were 60 years or older.

3.3 Use of AEDs and TCAs

We found that 34.2 % (n=297) of the patients in the period 2009–2011 used at least one AED and/or TCA. Table 6 shows the five most commonly prescribed drugs from this group. AEDs were prescribed most frequently for the treatment of pain/spasms, but there were also a few patients who used AEDs for epilepsy, bipolar disorder and migraine (Table 2 and 3). There were 20.5 % (n=178) of the patients who used at least two out of these five drugs. AEDs were prescribed to 25.7 % (n=223) of the patients for treatment of pain. The AEDs which were less frequently prescribed than carbamazepine are rarely used in pain treatment. For patients with MS, vice versa is also true; the most commonly prescribed AEDs/TCAs are almost exclusively prescribed for the treatment of pain. Of the AEDs described gabapentin and pregabalin are categorised as having very low propensity for pharmacokinetic interactions, clonazepam as moderate, while carbamazepine has a considerable potential for interactions. The less commonly prescribed AEDs are listed in table 7. There was considerable dosage variation, for example the maximum dosage of pregabalin was 18 times larger than the minimum dosage described. Gabapentin also showed large dosage variation, where the maximum dosage prescribed was 12 times larger than the minimum.

Table 6. Most commonly used AEDs and TCA 2009-2011

Drug	Drug class	N	Average dosage (mg)	Range (mg)	Bipolar diagnosis	Epilepsy diagnosis	Pain or spasms*	Propensity to interact
Gabapentin	AED	109	1517	300–3600		1		Very low
		12.5 %						
Clonazepam	AED	69	1	0.25–3		1	68	Moderate
		7.9 %						
Pregabalin	AED	66	341	50–900		1	65	Very low
		7.6 %						
Carbamazepine	AED	21	473	200–800	1	3	17	Substantial
		2.4 %						
Amitriptyline	TCA	84	30	10–75		1	83	-
		9.7 %						

*Pain/spasms was assumed when no other indication was reported. Propensities of AEDs to interact are based on review by Landmark and Patsalos 2010. TCA (tricyclic antidepressant); AED (antiepileptic drug)

Table 7. Less commonly used AEDs 2009-2011

Drug	N	Average dosage (mg)	Range (mg)	Bipolar disorder	Epilepsy diagnosis	Migraine	Mood disorder	Pain*	Propensity to interact
Lamotrigine	15	195	75–800		7		3	5	Substantial
Valproate	8	1029	600–1500	1	3	1		3	Substantial
Levetiracetam	3	1000	500–1500		3				Very low
Oxcarbazepine	3	1080	600–1440		1			2	Moderate
Phenytoin	2	150	100–200		2				Substantial
Topiramate	1	100	NA		1				Substantial
Phenobarbital	1	45	NA		1				Substantial

*Pain was assumed when no other indication was reported. Propensities to interact are based on review by Landmark and Patsalos 2010. TCA (tricyclic antidepressant); AED (antiepileptic drug)

Of the less commonly used AEDs all are considered as substantially likely to cause pharmacokinetic interactions, except for oxcarbazepine and levetiracetam, which propensities are categorised as moderate and very low, respectively.

3.3.1 Dosage variations of pregabalin versus gabapentin

To compare the dosage variability of gabapentin versus pregabalin, the dosages were normalised by dividing each value by the mean. Figure 7 shows a boxplot of the normalised dosages. The interquartile range (IQR) is about the same, but clearly the upper quartile of the gabapentin dosages are wider spread from the mean than the pregabalin dosages. The variances for the whole samples are not significantly different from one another.

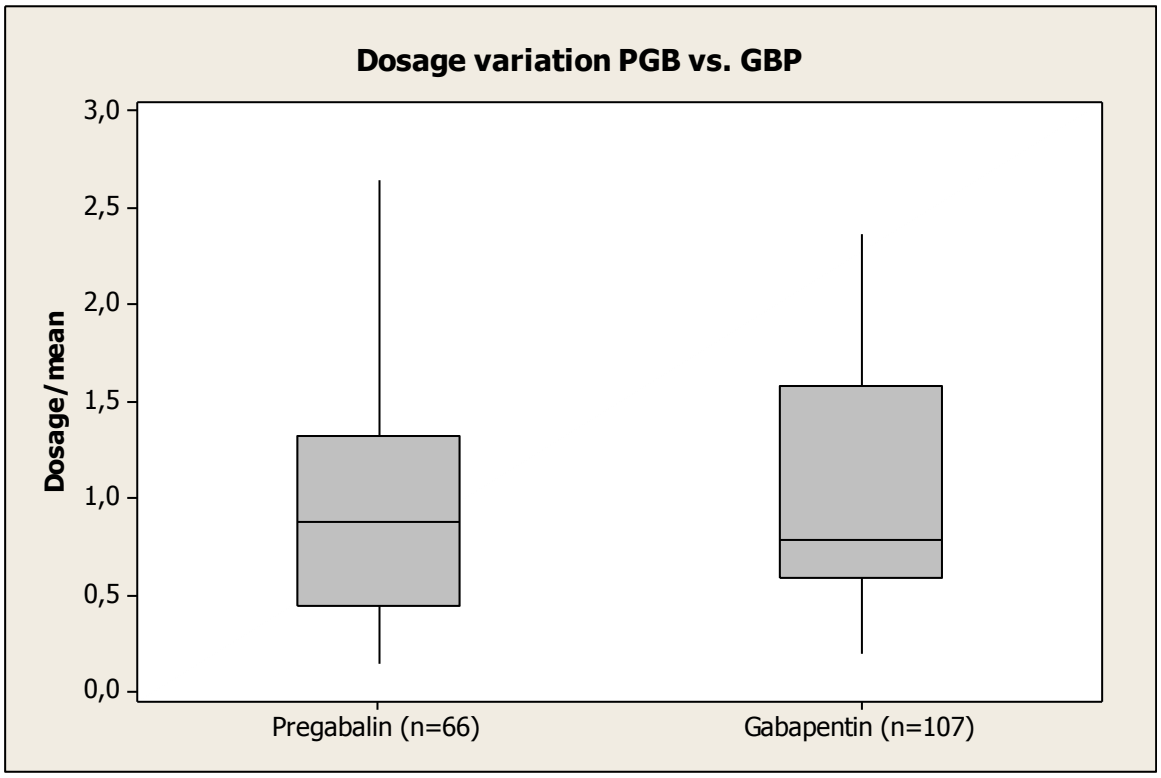


Figure 7. Dosage variation of PGB versus GBP

PGB (pregabalin); GBP (gabapentin)

3.3.2 Drug combinations with pregabalin and gabapentin

Different drug combinations with pregabalin or gabapentin were studied. We found that in the AED/TCA population, it is 77 % more likely that a patient using a Z-hypnotic also uses pregabalin, than that a patient not using a Z-hypnotic is using pregabalin. Fischer's exact test (for difference=0) was applied to test for significance in difference of the binomial distribution, the hypothesis was disproved with a p-value of 0.02. The same procedure was followed with gabapentin in combination with the Z-hypnotics, but the binomial distributions did not differ significantly.

Of the patients receiving oxycodone (n=9) in the AED/TCA population at MSSH, four used pregabalin, three gabapentin, one amitriptyline and one lamotrigine.

There was no correlation between use of opioids and pregabalin and/or gabapentin.

3.3.3 The development of use of AEDs and TCAs from 2009 to 2011

The development of the most commonly used AEDs/TCAs from 2009 to 2011, is displayed in figure 8. The use of gabapentin doubles from 2010 to 2011. Fischer's test was applied to test for significance in difference between the distribution of gabapentin users and non-users, for 2010 versus 2011. The test proved that the distribution is significantly different in 2010 as compared to 2011 (p=0.02).

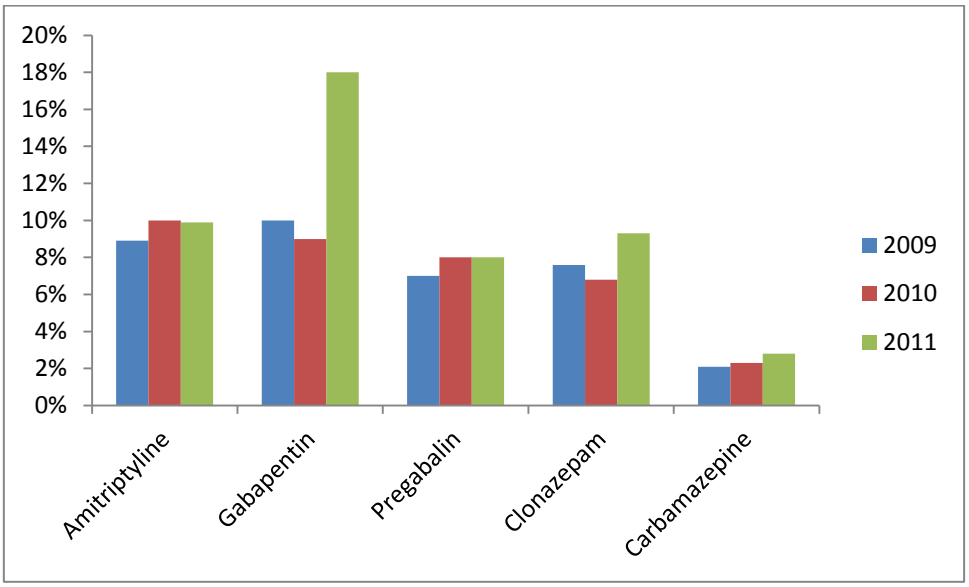


Figure 8. AEDs and TCA used for treatment of neuropathic pain 2009-2011

TCA (tricyclic antidepressant); AED (antiepileptic drug)

3.4 Aspects of polytherapy

3.4.1 Drug count distribution

The average patient in the AED/TCA subpopulation uses a total of 5.36 (1–19) different prescription drugs. The drug count distribution is shown in figure 9. In the AED/TCA subpopulation 57 % of the patients used 5 or more drugs and 6.7 % of patients were using 10 drugs or more.

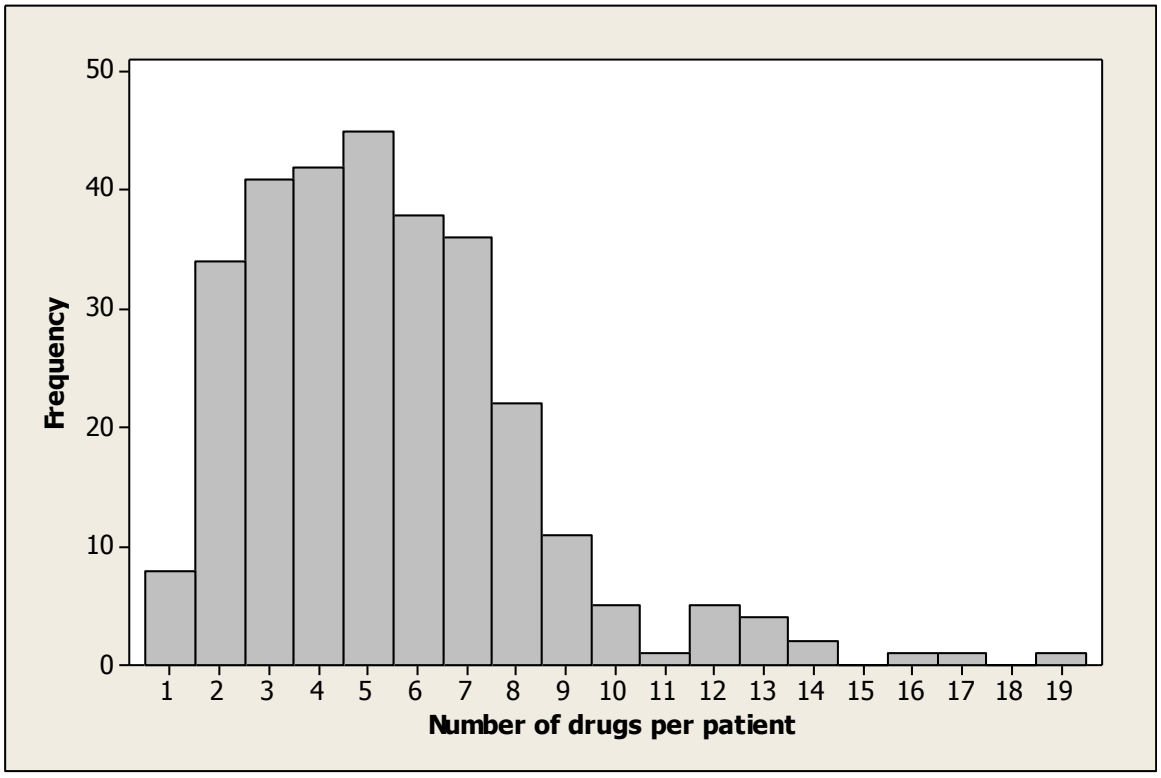


Figure 9. EDSS distribution

3.4.2 Most commonly used prescription drugs

On average men used 4.7 drugs each, while women used 5.6. The only drug prescribed significantly different to men and women was mirtazapine, with some exceptions such as hormones. Mirtazapine was used by four men, but only by one woman; keeping in mind that the population includes about twice as many women as men, this is a substantial difference (Fischer's test, p=0.02). It is worth mentioning that natalizumab showed a tendency towards being more commonly prescribed in women than men, although non-significant (p=0.06). The 15 most commonly used prescription-drugs are listed in table 8 with corresponding rankings for women and men respectively.

Table 8. Top 15 prescription drugs

	Drug	N (297)	Indication	Ranking for women	Ranking for men
1.	Gabapentin	36.7 %	Neuropathic pain	1.	1.
2.	Baclofen	27.6 %	Spasms	2.	2.
3.	Amitriptyline	28.3 %	Neuropathic pain	3.	3.
4.	Clonazepam	23.6 %	Spasms/pain, insomnia	5.	4.
5.	Pregabalin	22.2 %	Neuropathic pain	4.	5.
6.	Tolterodine	15.2 %	Bladder dysfunction	6.	7.
7.	Methenamine Hippurate	13.1 %	Urinary antiseptic	7.	8.
7.	Solifenacin	13.1 %	Bladder dysfunction	9.	6.
7.	Zopiclone	13.1 %	Insomnia	11.	10.
10.	Interferon-beta	11.8 %	Relapsing-remitting MS	8.	11.
11.	Levothyroxine	10.8 %	Low metabolism	9.	18.
11.	Simvastatin	10.8 %	High cholesterol	10.	14.
12.	Codein + acetaminophen	9.4 %	Pain	16.	10.
13.	Acetylsalisylic acid	9.1 %	Anticoagulant	17.	9.
14.	Glatiramer Acetate	8.8 %	Relapsing–remitting MS	13.	14.
15.	Natalizumab	8.1 %	Relapsing–remitting MS	12.	27.

3.4.3 Comedication affecting the CNS

As described in section "2.5 Study scope", some drug classes were of special interest and their prescription is summarised in table 9. Half of the patients use at least one benzodiazepine (excluding clonazepam, which was defined as an AED), an opioid or baclofen in addition to their AED/TCA treatment. The combined use of A and B opioids includes 62 unique patients, representing 20.9 % of the AED/TCA subpopulation. The patients using opioids in the AED/TCA subpopulation had a significantly higher median EDSS score than the other AED/TCA patients (Mann-Whitney test: $EDSS_{opioid}$=5.5; n=33 and $EDSS_{non\text{-}opioid}$=4.5; n=103; p=0.01; W=2757.5). There was an 8–9 fold dosage variation of baclofen, tramadol and escitalopram (table 9).

Table 9. Comedication affecting the CNS

	N (%)	N	Average dosage (mg)	Range (mg)	Indication
Alpha-2 blockers	2.0 %	6			Depression
Mianserin		1	30	(30)	
Mirtazapine		5	27	(15–30)	
Antispasmodic	27.5 %	82			Spasm
Baclofen		82	32.8	(10–90)	
Opioids A*	7.4 %	22			Pain
Oxycodone		9	24.5	(10–54)	
Buprenorphine		4	NA		
Other		14			
Opioids B*	14.4 %	43			Pain
Codeine		30	NA		
Tramadol		15	252.3	(50–400)	
SSRI/SNRI	17.8 %	53			Depression
Escitalopram		18	14.7	(5–40)	
Citalopram		17	23.5	(10–40)	
Venlafaxine		7	128.6	(75–225)	
Other		11			
Benzodiazepines**	18.9 %	56			
Diazepam		12	8.5	(4–15)	Anxiety
Zopiclone		38	6.7	(2.5–7.5)	Insomnia
Zolpidem		9	10.6	(10–15)	Insomnia
Central stimulants					
Modafinil		5	160	(100–200)	Narcolepsy Fatigue

**describing Norwegian prescription classes; **Benzodiazepines excluding clonazepam*

3.5 Disease-modifying treatment

An overview of the disease-modifying treatment of patients in the period 2009–2011 is given in table 10. In 2009, patients receiving beta-interferon and patients not receiving beta-interferon were treated equally often with AEDs/TCA (30.8 % and 33.5 %, respectively).

Table 10. Disease-modifying treatment 2009-2011

	2009	2010	2011
Population	General	AED/TCA	AED/TCA
N	236	97	126
Disease-modifying treatment	31.8 %	31.0 %	31.0 %
1st line-treatment (beta-interferon, glatiramer acetate)	82.7 %	66.7 %	56.4 %
2nd line-treatment (natalizumab, fingolimod)	14.7 %	30.0 %	35.9 %
3rd line-treatment (mitoxantrone)	2.7 %	3.3 %	7.7 %

The use of first-line treatment was predominant in all inclusion years. Although the proportion of MSSH patients treated with disease-modifying drugs remained constant, use of second- and third-line treatment increased throughout the inclusion years. The mean amitriptyline dosage in the interferon-beta population was 36.9 (n=13), and in the non-interferon-beta population it was 29.2 (n=63). The 2-sample t-test showed that the difference in mean amitriptyline dosages was not significant (p=0.25).

4. Discussion

4.1 Discussion of results

This study adds to the research on pharmacological treatment of pain in MS, while it focuses on the rationale of the treatment with AEDs and TCAs in light of polypharmacy issues. Relating pharmacological treatment to patients' degree of disability with a special focus on pain therapy is a new approach to apply current knowledge of evidence-based medicine for the benefit of MS patients.

There is a wide span of symptomatic treatment options applied to improve the quality of life of MS patients. Pain is a very common and disabling symptom. One in every three patients in the general MSSH population is treated pharmacologically to relieve pain, including patients of all ages, genders and degrees of disability. In a study of pain in 142 MS patients, 65 % reported that they experienced pain (Beiske et al. 2004). It was also found that the pain was independent of demographic variables. However, only one third of the patients were treated for their pain. It is unlikely that the prevalence of pain has changed in the last ten years, so it seems that more patients are receiving treatment.

4.1.1 Demographics

General MSSH population

The mean age of the population was 55.4 years. A comparable statistic from another cross-sectional Norwegian MS population has not been found, since it is more common to report the average age at disease onset. Age at disease onset was not registered in this study since it is rarely in found in medical records. By combining the reported age at disease onset and average disease duration, the average age of an MS population in eastern Norway was calculated to be 49.8 years (n=140) (Beiske et al. 2008).

The frequency of men in the general MSSH population increases substantially from the 30–39 age group to the 40–49 age group, this is likely explained by the fact that PPMS is more common in men, because the mean age of PPMS onset is about 40 years (Myhr et al. 2001). This also explains why the proportion of women is higher in the age group 30-39. The increase in frequency of women in the age group 50–59 compared to the 40–49 group, may be

explained by the fact that they have older children. A stay at MSSH is usually four weeks long and this may be considered too long by women with younger children at home.

The EDSS distribution characterises the general MSSH population with regards to function level and thereby provides a means to compare the population with other populations as well. We can tell that a broad spectre of patients have stayed at MSSH in the inclusion years. The peaks at score 4.0 and 6.5 are typical for cross-sectional studies of MS populations. Myhr et al. (2001) described the same peaks (2.0–3.5; 6.0–8.0; n=220) in his study of MS patients in Hordaland county and explained that they are consequences of the disease course; at these function levels the disability progresses slower. The mean EDSS score of the Hordaland population was 4.5 ± 0.2 (s.e.), the MSSH population's mean EDSS score was 4.75 ± 0.1. The MSSH population seems to be representative of the geographically determined Hordaland population with regards to degree and distribution of disability. This observation suggests, that we may allow for our results to be projected on to other MS populations. Comparing the disability distributions of the two populations is especially important to this study, since it provides a means for quality assurance by controlling eventual inclusion bias. For example, the main intake criteria at MSSH (potential for rehabilitation) could be a cause of such.

Prevalence of epilepsy

The MSSH population had a prevalence of epilepsy of 2.6 %. This is two to three times the prevalence of epilepsy in the general population and is in accordance with previous studies (Koch et al. 2008). Etemadifar et al. studied the demographics of their EP/MS (epileptic MS) population versus their non-EP/MS population looking for a possible link explaining the increased epilepsy prevalence. They found that the frequency of EOMS in the EP/MS population was twice that of the EOMS frequency in the non-EP/MS population (12.3 and 5.9 %, respectively). Neuroimaging studies have related cortical and subcortical lesions to ictal behaviour and this is the most commonly supported hypotheses for explaining the increased epileptic seizure prevalence (Truyen et al. 1996).

The distribution of EDSS (bi-modal), gender, age and epilepsy prevalence all indicate that a representative MS population has been included in this study.

AED/TCA subpopulation

To elucidate the potential polypharmacy issues related to the use of AEDs and TCAs it is appropriate characterise the population using them. Does this population differ from the population of MS patients not using AEDs or TCAs?

The epilepsy prevalence in the AED/TCA subpopulation is higher than in the general MSSH population (7.7 and 2.6 %, respectively); still more than 90 % of the population are using the drugs for other indications than epilepsy. We have shown that the AEDs and TCAs are primarily used for treating pain. There is no difference in age, gender or degree of disability when comparing the general MSSH population and the AED/TCA subpopulation.

4.1.2 Use of AEDs and TCAs

Antiepileptic drugs

Gabapentin and pregabalin were the most frequently prescribed drugs for continuous treatment of pain in the AED/TCA subpopulation. Although more patients were using clonazepam than pregabalin, many of the patients using clonazepam are using it sporadically. In a national study of prescriptions in Norway, throughout 2007, pregabalin was the most prescribed AED and gabapentin the second most prescribed AED for treatment of neuropathic pain (Johannessen Landmark et al. 2009).

From 2010 to 2011 the proportion of patients using gabapentin at MSSH doubled. The explanation for this dramatic difference may be an indirect effect coming from a change of the refund policy as of May 1st, 2009, by Norwegian health authorities on pregabalin prescriptions (HELFO 2009). The new regulation demanded that all patients had to try gabapentin before they could be given pregabalin, most likely because pregabalin is more expensive. Prescriptions are typically valid for one year, delaying the effect of this regulatory change. It is not unlikely that gabapentin since then has overtaken pregabalin as the most common AED for neuropathic pain nationally. In MS, pregabalin and gabapentin can also be used to treat spasms in addition to baclofen in cases difficult to treat (Beiske 2009).

A recent Cochrane review on gabapentin for chronic neuropathic pain and fibromyalgia concluded that adverse effects of gabapentin are common, but mild (Moore et al. 2011). Only one in every ten patients stopped treatment due to adverse reactions. The Cochrane review did

not focus on central pain and therefore the authors conclusions on efficacy do not apply to MS related neuropathic pain. The European Federation of Neurological Societies (EFNS) classify pregabalin as level A and gabapentin as level A/B with regards to efficacy in central pain and both are recommended as first-line treatment (Attal et al. 2010).

Even though the effects of gabapentin and pregabalin are similar in most patients, a reduced uptake of gabapentin has been shown in as many as 40 % of patients (Gidal et al. 2000). Those 40 % may fail treatment with gabapentin or require higher dosages than other patients. Since pregabalin does not have the same issue, we suspected that we might find a larger variation in the dosages of gabapentin as compared to pregabalin. The gabapentin dosage distribution did have a right-sided tail, which could be caused by a reduced gastrointestinal absorption in some patients.

Tricyclic antidepressants

Less than five patients were treated for depression with a TCA, therefore this indication for TCAs will be discussed no further. The only TCA used for treatment of pain was amitriptyline. The EFNS guidelines recommend amitriptyline as first-line treatment for central pain (Attal et al. 2010). In addition to the regular tablets, there is also a depot formulation available. Most medical records included the regular tablets, but some did specify that the depot formulation was being used. Either the prescribing doctors should be more precise when writing medical records or many patients may benefit from changing to the depot formulation. Especially when there is a potential for pharmacodynamic interactions, a depot formulation which reduces C_{max} can reduce the magnitude of peak concentration related adverse reactions. The involvement of β_2-adrenoceptors in TCA's mechanism of action for relieving neuropathic pain suggests an incompatibility with beta-blockers that affect these receptors (Yalcin et al. 2009). This may be an important notion considering the number of patients treated with amitriptyline and switching to a different antihypertensive should be simple.

4.1.3 Comedication affecting the CNS

SSRIs and SNRIs

SSRIs/SNRIs were used by 18 % of the AED/TCA subpopulation. These drugs are mainly used to treat depressions, which are twice as common among MS patients as in the general population (Beiske et al. 2008). The study of 140 Norwegian MS patients also showed that 31.4 % had symptoms of depression and that only 15.9 % of them were receiving treatment.

There were surprisingly large variations in the dosages of citalopram (10–40 mg) and escitalopram (5–40 mg) in the AED/TCA subpopulation. Dosages of more than 20 mg escitalopram per day have not been tested with regards to safety and should in general not be given (SmPC-escitalopram 2013). Although SSRI/SNRIs are useful in treatment of peripheral neuropathic pain since they are generally better tolerated than TCAs, they have never been proven efficacious for treatment of central neuropathic pain (Attal et al. 2010). The dosage variation may still be a result of attempting treatment of pain or depression.

Opioids

Opioids were used by 21 % of the AED/TCA subpopulation. Opioids are considered the last resort for long-term pain management due to the likely development of tolerability and risk of dependence. This is confirmed by our finding that the patients receiving opioids in addition to an AED or TCA have significantly higher EDSS scores than AED/TCA patients who are not receiving opioids. Dependence issues are less commonly associated with "B group" opioids (tramadol and codeine) than "A group" opioids (oxycodone, buprenorphine etc.). Large dosage variations were seen with tramadol treatment (50–400 mg). Adjusting dosages to the minimum which still provides satisfactory pain-relief is important when opioids are applied in long-term treatment. This will reduce common adverse effects such as constipation and also reduce development of tolerability. Tramadol inhibits noradrenaline reuptake in addition to binding the μ-opioid receptor. Therefore it has a better dose-effect ratio compared to morphine for treatment of neuropathic pain than it has compared to morphine for treatment of nociceptive pain (Smith 2012).

Controlled-release oxycodone and pregabalin in combination for treatment of non-cancer pain proved efficacious and was recommended after a one-year long study of more than 1000 patients (Gatti et al. 2011). A recent Cochrane review concluded that gabapentin in

combination with an opioid provides better pain-relief than gabapentin alone in both peripheral and central neuropathic pain, but adverse reactions were also more common (Chaparro et al. 2012).

Benzodiazepines

Clonazepam is particularly interesting when it comes to treatment of MS patients. As a sedative or an antiepileptic it is not considered first- or second-line. However, clonazepam's sedative, antispasmodic and pain relieving effects combined make it useful for MS patients in the evening.

There have been reports of use misuse of pregabalin and gabapentin (Caster et al. 2011, Prescrire 2012). Therefore we wanted to see if these drugs were more commonly used in combination with other drugs with a sedative effect and a potential for misuse. Our finding that it is much more likely for a patient using a Z-hypnotic to be using pregabalin than any other patient in the AED/TCA population adds to this. Furthermore, it highlights the possible presence of a pharmacodynamic interaction.

4.1.4 Disease-modifying treatment

With new and increasingly expensive disease-modifying drugs becoming available during the last decade, there has been an ongoing debate on their funding. There are those who believe that the availability of disease-modifying treatment is unequal throughout the country, which is unacceptable for the social democracy. "The economic model for funding the costs of these drugs forces hospitals to choose the cheapest available option", according to health economist Bjørn Svendsen (Nordahl 2012). Second-line treatment options (fingolimod and natalizumab) are more expensive, but have proven to reduce more attacks. Nationally 43 % of patients are treated with first-line drugs and 13 % with second-line drugs in 2011 (Link-Medical 2012). In the 2011 AED/TCA population at MSSH 17 % received first-line treatment and 11 % second-line treatment. Nationwide, 56 % of patients were receiving disease-modifying treatment, while this only was true for 31 % of the patients at MSSH. The large difference may come from a difference in proportion of RRMS patients, but this is difficult to determine as we don't have these data available. The MSSH population may be older than the national

MS population, providing a shift from RRMS to SPMS patients and thus lowering the proportion treated with disease-modifying drugs.

The average dosages of the comedication used by the population of interferon-beta users was studied, because it has been shown that interferon-alpha inhibits CYP enzyme activity (Christensen and Hermann 2012). Amitriptyline was the only drug metabolized by CYP enzymes, for which we possibly had a large enough sample size to compare dosages of interferon and non-interferon receiving patients (Olesen and Linnet 1997). In contrast to what was expected, the amitriptyline dosages of the interferon-beta users were actually insignificantly higher than the corresponding dosages of the non-interferon-beta users.

4.1.5 Polytherapy considerations

Pharmacokinetic and -dynamic interactions

Even though the patients at MSSH frequently used AEDs in combination with other drugs, they rarely used the AEDs most susceptible to drug related problems. Instead they used the newer generation AEDs, gabapentin and pregabalin. These drugs are not associated with pharmacokinetic interactions like the AEDs of the previous generation (Johannessen Landmark and Patsalos 2010). Patients with epilepsy and MS require more attention since they use a wider range of AEDs.

A recent Cochrane review on combination treatment of neuropathic pain reported that the number of drop-outs due to adverse reactions often was higher in combination therapy and that this limits its application. One fifth of the general MSSH population used at least two of the included AEDs/TCAs and more than half of the AED/TCA subpopulation used an opioid, a benzodiazepine (other than clonazepam) or baclofen. All of which are drugs that can cause sedation and general CNS depression, just like gabapentin, pregabalin and amitriptyline. Considering that fatigue is one of the most common MS symptoms affecting 75 % of patients (Hadjimichael et al. 2008), these pharmacodynamic interactions are likely to be clinically relevant. Such interactions may affect the patient's reaction time and thus ability to drive or operate heavy machinery. The Norwegian Directorate of Health suggest halving the maximum dosages regarded as safe for driving when combining two drugs from their list of drugs that require attention (Helsedirektoratet 2006). The clinician's assessment of the individual patient's ability to drive supersedes the recommendations given by the guideline.

The applied recommendations of today limit the possibility of many of the included patients in the study to drive a car. A consideration of applying serum concentration measurements instead of dosage could adjust for extensive pharmacokinetic variability among patients.

Pharmacokinetic variability

Pharmacokinetic and pharmacodynamic interactions may be further potentiated by interindividual differences. Pharmacokinetic variability includes a number of important parameters that need to be considered in the individual patient. Genetic variations between individuals result in different capacity of enzyme activity which can alter clearance (Lesko and Schmidt 2012). Obesity may affect serum concentrations, as the volume of distribution of lipid-soluble drugs increases. Age changes physiological and thus pharmacokinetic parameters such as clearance and half-life. One third of the patients in the AED/TCA subpopulation were 60 years or older. These patients generally have lower renal clearance and may therefore require lower dosages. We know that the most commonly daily used AEDs, gabapentin and pregabalin, are unlikely to cause pharmacokinetic interactions partly because they are excreted renally. In patients with reduced renal clearance, however, they require attention and certainly when combined with other CNS-depressing drugs. If this is not considered, they are more likely to suffer from adverse reactions and pharmacodynamic interactions in particular.

When physiological parameters vary greatly and therapeutic windows are small, as exemplified above, it is apparent that pharmacologic treatment should vary too. The 18-fold dosage variation described for pregabalin displays the wide range of variability.

Treatment challenges and clinical implications

Neuropathic pain is difficult to treat and central neuropathic pain, in particular. The drug distribution showed that 6.7 % of the patients in the AED/TCA subpopulation were using ten drugs or more and that 57 % of the patients were using five drugs or more. This elucidates the vast potential for polypharmacy issues, such as compliance, interactions and adverse reactions. Poor compliance may be caused by cognitive effects, which can be improved by a pill organiser or single-dose packing, or it may be intentional as a result of adverse reactions. Drug treatment may be initiated by the patient's personal physician, personal neurologist or

MSSH's neurologist and drug tapering may be difficult if treatment was initiated by another doctor.

The pharmacologic treatment of MS patients today relies mainly on clinical observations. Baclofen dosages are finely tuned this way. Patients with spasms and highly limited leg muscle function may depend on the constriction of their leg muscles by the spasms to be able to stand. While it may be painful, it can still be of major importance to the patient. If this patient would use more baclofen she would lose the ability to stand. Whereas a patient permanently restricted to a wheelchair would prefer a much higher dosage, better relieving the painful spasms (Beiske 2013).

In other disorders where therapeutic windows are narrow, measuring serum concentrations of the drugs is used as a tool for achieving optimal dosages; this is termed therapeutic drug monitoring (TDM). TDM is useful because achieving an individually optimal serum concentration is of vital importance when adverse reactions can be serious (Budde and Glander 2008). When antiepileptic drugs are used to treat epilepsy or psychiatric disorders, TDM is routinely utilised in Norway (Bengtsson 2004, Patsalos et al. 2008, Lesko and Schmidt 2012). Close monitoring of AEDs by implementation of therapeutic drug monitoring may control for pharmacokinetic variability and -interactions (Patsalos et al. 2008). This is also important to consider for psychotropic drugs, as it has been demonstrated that female gender and old age are important factors contributing to pharmacokinetic variability and lower serum concentrations of antidepressants (Waade et al. 2012). An alternative implementation of TDM is for example in immunosuppressive treatment with mycophenolate (Vethe et al. 2008). The increasing use of TDM has allowed for development of TDM databases which act as a reference for targeting serum concentrations, improving treatment and reducing adverse reactions. When applying the concept of an individual therapeutic concentration in the single patient, TDM could also be useful when these antiepileptic drugs are used in the treatment of neuropathic pain (Johannessen and Landmark 2008).

4.2 Discussion of method

This study aimed to examine use of AEDs and TCAs in pharmacological treatment of pain in MS, in light of polypharmacy issues. Relating pharmacological treatment to patients' degree of disability with a special focus on pain therapy is a new approach to apply current knowledge of evidence-based medicine for the benefit of MS patients. The method chosen, provided a relatively large population and the data was electronically available allowing efficient data gathering. A downside to retrospective studies of medical records is however, the lack of information in the medical records. An example of this in our study, proved to be the availability of EDSS scores. Only 343 of 869 medical records included an EDSS score. Every patient staying at MSSH is assigned an id number by the administration. There is no way to link the patient's id number to their identity without access to the Extensor database. Therefore these id numbers were registered directly in the study spread sheet. The benefit of utilising MSSH's patient id numbers was that there never was created a document which could identify the patient data.

Examining prescriptions to a large population may also uncover new potential interactions, both pharmacodynamic and pharmacokinetic (Johannessen Landmark and Patsalos 2012). The importance of such aspects of these studies, are highlighted by the limitations of phase III clinical trials with regards to inclusion criteria and study duration. Both positive and negative results of this study may be utilised to benefit the patient population.

The use of amitriptyline was defined as an inclusion criterion, since it is used frequently in treatment of neuropathic pain. AEDs were included regardless of their indication, because the link of increased epilepsy prevalence in MS adds another interesting aspect to the investigation of their use. Other TCAs than amitriptyline (e.g. TCAs not used for neuropathic pain) were not defined among these inclusion criteria. Data on the use of other TCAs were registered when coadministered with a drug on the list of inclusion criteria, in line with other concomitantly used drugs, but the extent of use was limited.

4.3 Future prospects and concluding remarks

Future prospects

Sativex was recently approved (28th Nov 2012) for treatment of spasms in Norway, however, since no patients were using it in the inclusion period it was not discussed in great detail in this thesis. Cannabinoids have also been proven efficacious in MS related pain by vigorous studies, but their spectre of adverse reactions has yet to be fully determined and they have not been proven superior to other treatment options (Solaro and Uccelli 2011).

Extending the study to include patients with a stay at MSSH in 2012 would be of value as it could address questions based on current results. Will the doubling of gabapentin prescriptions from 2010 to 2011 stabilise or keep increasing? Including 2012 in the study would also provide data on the use of the new drugs Sativex and Fampyra (fampridine). Fampyra is potassium channel blocker and more than 100 patients at MSSH used it in 2012. It is applied to improve walking distance in MS patients, however as its action on neurons is opposite of AEDs we suspect it may have an impact on pain treatment.

Conclusion

This study has shown that one third of MS patients used either an AED or TCA and that one fifth used two or more. There was no difference in age, gender or degree of disability of the patients using these drugs. Pain is a common and debilitating symptom and polytherapy is widespread, with up to 19 concomitant drugs in use. Although the AEDs are well-known for their pharmacokinetic interactions, this is not particularly concerning for MS patients since they mainly used newer AEDs (pregabalin and gabapentin) with little propensity to interact. Pharmacodynamic interactions are of greater concern seeing as more than half of the patients used an opioid, a benzodiazepine or baclofen in addition to their AED/TCA therapy. One third of the patients were elderly and careful considerations regarding pharmacokinetics and possible excessive adverse reactions are of importance.

Applying therapeutic drug monitoring when using AEDs and TCAs for treatment of neuropathic pain is worth considering, seeing as it has been so valuable in treatment of epilepsy. To reduce the total drug load or dosages of CNS-active drugs may also be important in many patients. The results in this study add to the research on pharmacological treatment of

pain in MS and call for risk/benefit studies of pain treatment in light of pharmacodynamic interactions and interindividual variability.

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6. Appendix

6.1 EDSS scores

Appendix B. Expanded Disability Status Scale (EDSS)

0 = Normal neurologic exam (all grade 0 in Functional Systems [FS]; Cerebral grade 1 acceptable).

1.0 = No disability, minimal signs in one FS (ie grade 1 excluding Cerebral grade 1).

1.5 = No disability minimal signs in more than one FS (more than one grade 1 excluding Cerebral grade 1).

2.0 = Minimal disability in one FS (one FS grade 2, others 0 or 1).

2.5 = Minimal disability in two FS (two FS grade 2, others 0 or 1).

3.0 = Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory.

3.5 = Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1).

4.0 = Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 500 meters.

4.5 = Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 meters.

5.0 = Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (eg, to work full day without special provisions). (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0.)

5.5 = Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0.)

6.0 = Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk about 100 meters with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)

6.5 = Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 meters without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)

7.0 = Unable to walk beyond about 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in w/c some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone.)

7.5 = Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+.)

8.0 = Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems.)

8.5 = Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions. (Usual FS equivalents are combinations, generally 4+ in several systems.)

9.0 = Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+.)

9.5 = Totally helpless bed patient; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+.)

10. = Death due to MS.

6.2 Letter of confirmation of ethical approval from MSSH

ms-senteret
HAKADAL AS

Bekreftelse på innvilget søknad om etisk godkjenning av prosjektet:

"Kvalitetssikring av medikamentell behandling hos pasienter ved MS Senteret Hakadal – en retrospektiv studie med vekt på polyfarmasi og mulige interaksjoner med antiepileptika"

Søker: Georg Beiske (student) og Cecilie Johannessen Landmark (prosjektansvarlig)

For å gjennomføre prosjektet gis Georg Beiske adgang til pasientjournaler i perioden 01.05.12-15.02.13. Georg Beiske må skrive under MSSH's taushetserklæring og har kun tillatelse til å hente ut følgende opplysninger fra pasientjournalene:

-Fødselsdato

-Kjønn

-Medikasjon

-Komorbide lidelser

-EDSS

Dataene lagres anonymisert.

Hakadal den 16.04.2012

Antonie Giæver Beiske

Daglig leder MSSH, PhD

MS-Senteret Hakadal AS
Et aksjeselskap 100 % eid av
MS-forbundet i Norge

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