European Journal of Neurology

EAN Guideline on Palliative Care of People with Severe, Progressive Multiple Sclerosis

Solari A*, Giordano A, Sastre-Garriga J, Köpke S, Rahn AC, Kleiter I, Aleksovska K, Battaglia MA, Bay J, Copetti M, Drulovic J, Kooij L, Mens J, Meza Murillo ER, Milanov I, Milo R, Pekmezovic T, Vosburgh J, Silber E, Veronese S, Patti F, Voltz R, and Oliver DJ, on behalf of the guideline task force

*** Corresponding author**

Alessandra Solari, MD

Unit of Neuroepidemiology

Fondazione IRCSS Istituto Neurologico Carlo Besta, Milan, Italy

E-mail: alessandra.solari@istituto-besta.it

Appendix 5: Report of recommendations pertaining to clinical questions 3 to 10

Contents

1. Advance care planning (clinical question 3)

According to the European Association of Palliative Care, advance care planning (ACP) is a process that "enables individuals who have decisional capacity to identify their values, to reflect upon the meanings and consequences of serious illness scenarios, to define goals and preferences for future medical treatment and care, and to discuss these with family and healthcare professionals (HPs). ACP addresses individuals' concerns across the physical, psychological, social, and spiritual domains. It encourages individuals to identify a personal representative and to record and regularly review any preferences, so that their preferences can be taken into account should they, at some point, be unable to make their own decisions" [Rietjens 2017].

Of 617 records screened, 7 were assessed as full text [Buecken 2012, Chen 2013, McCurry 2013, Brinkman-Stoppelenburg 2014, Golla 2015, Golla 2016, Leclerc-Loiselle 2018] and excluded from the final selection.

As from a systematic review [Brinkman-Stoppelenburg 2014], there is no evidence of the effects of ACP for patients with neurological diseases, including multiple sclerosis (MS). However, there is some evidence from other progressive and life-threatening illnesses that ACP decreases the use of life-sustaining treatment, increases hospice/PC, reduces hospitalizations and increases compliance with patients' end of life wishes [Brinkman-Stoppelenburg 2014].

Concerning MS, there is evidence that patients and caregivers often would like to discuss the issues of death and dying and HPs should acknowledge and encourage these discussions [Golla 2015, Golla 2016]. Often professionals leave discussions until the later stages of progression in MS [Walter 2019]. Patients react in different ways on discussion of future planning. A small study showed that some MS patients made clear decisions, some undertake some planning but without a clear advance directive and some were still "hoping for a cure" and did not wish to look ahead [Chen 2013]. However, caregivers may be left having difficult decisions if no planning has taken place and this was stressful for caregivers [McCurry 2013].

References

Brinkman-Stoppelenburg A, Rietjens JAC, van der Heide A. The effects of advance care planning on end-of-life care: A systematic review. Palliat Med 2014; 28(8): 1000–1025.

Buecken R, Galushko M, Golla H, et al. Patients feeling severely affected by multiple sclerosis: How do patients want to communicate about end-of-life issues? Patient Educ Couns 2012; 88: 318-324.

Chen H, Habermann B. Ready or not: planning for health declines in couples with advanced multiple sclerosis. J Neurosci Nurs 2013; 45: 38–43.

Golla H, Mammeas S, Galushko M, Pfaff H, Voltz R. Unmet needs of caregivers of severely affected multiple sclerosis patients: A qualitative study. Palliat Support Care 2015; 13(6): 1685–1693.

Golla H, Galushko M, Strupp J, et al. Patients feeling severely affected by multiple sclerosis: addressing death and dying. Omega: Journal of Death & Dying 2016; 74(2): 275–291.

Leclerc-Loiselle J, Legault A. Introduction of a palliative approach in the care trajectory among people living with advanced MS: perceptions of home-based health professionals. Int J Palliat Nurs 2018; 24: 264–270.

McCurry MK. An exploratory study of decision making by informal caregivers of individuals with multiple sclerosis. J Neurosci Nurs 2013; 45(1): 52–60.

Rietjens JAC, Sudore RL, Connolly M, et al. Definition and recommendations for advance care planning: an international consensus supported by the European Association for Palliative Care. Lancet Oncol. 2017; 18(9): e543-e551.

Walter HAW, Seeber AA, Willems DL, de Visser M. The role of palliative care in chronic progressive neurological diseases-a survey amongst neurologists in the Netherlands. Front Neurol 2019 14; 9: 1157.

2. Patient discussion with healthcare professionals of their wish to hasten death (clinical question 4)

HPs' acknowledgment of, and open discussion about, the patient's wish to hasten death and related issues emerged as key from both TF members (chiefly PC physicians) and MS patients [Köpke 2019].

Of 491 records screened, 7 were assessed as full text [Berkman 1999, Hall 2005, McCrone 2009, Buecken 2012, Golla 2016, Strupp 2016, Marrie 2017] and excluded from the final selection.

We found no evidence regarding the effects of discussing with HPs the wish to hasten death. However, in a study conducted over 20 years ago, Berkman et al. reported that 33% of patients with MS considered suicide or assisted dying [Berkman 1999]. In recent studies, 22% of MS patients had suicidal intention [Strupp 2016], and 7% would consider suicide and 65% assisted dying if they had unbearable pain [Marrie 2017]. Suicidal ideation or consideration of assisted dying was related to depression, hopelessness, the MS affecting leisure time and feeling socially isolated [Hall 2005, Strupp 2016]. Access to PC expertise has been recommended for individuals requesting euthanasia or physician assisted suicide as further assessment and management of symptoms or psychosocial or spiritual distress [Radbruch 2016].

In somatically severely ill, incurable patients, suffering from psychiatric conditions, proactively addressing a possible desire to die can reduce suffering [DeCou 2018, Blades 2018].

References

Berkman CS, Cavallo PF, Chesnut WC, Holland NJ. Attitudes toward physician-assisted suicide among persons with multiple sclerosis. J Palliat Med 1999; 2(1): 51–63.

Blades CA, Stritzke WGK, Page AC, Brown JD. The benefits and risks of asking research participants about suicide: A meta-analysis of the impact of exposure to suicide-related content. Clinical Psychology Review 2018; 64: 1-12.

Buecken R, Galushko M, Golla H, et al. Patients feeling severely affected by multiple sclerosis: How do patients want to communicate about end-of-life issues? Patient Educ Couns 2012; 88: 318-324.

DeCou CR, Schumann ME. On the iatrogenic risk of assessing suicidality: a meta-analysis. Suicide Life Threat Behav 2018; 48(5): 531-43.

Hall L. Factors that predict desire for hastened death in individuals with Multiple Sclerosis. Dissertation Abstracts International: Section B: The Sciences and Engineering 2005; 66(4–B): 2307.

Golla H, Galushko M, Strupp J, et al. Patients Feeling Severely Affected by Multiple Sclerosis: Addressing Death and Dying. Omega: Journal of Death & Dying 2016; 74(2): 275–291.

Köpke S, Giordano A, Veronese S, et al. Patient and caregiver involvement in formulation of guideline questions: Findings from the EAN guideline on palliative care of people with severe multiple sclerosis. Eur J Neurol 2019; 26(1): 41-50.

McCrone P. Capturing the costs of end-of-life care: comparisons of multiple sclerosis, Parkinson's disease, and dementia. J Pain Symptom Manage 2009; 38(1): 62–67.

Marrie RA, Salter A, Tyry T, et al. High hypothetical interest in physician-assisted death in multiple sclerosis. Neurology 2017; 88(16): 1528–1534.

Radbruch L, Leget C, Bahr P, et al. Euthanasia and physician-assisted suicide: A white paper from the European Association for Palliative Care. Palliat Med. 2016;30(2):104-16.

Strupp J, Voltz R, Golla H. Opening locked doors: Integrating a palliative care approach into the management of patients with severe multiple sclerosis. Mult Scler 2016; 22: 13-18.

3. Symptom management (clinical question 5)

This patient population is characterized by the presence of several symptoms, in variable combination between patients and in a same patient over time (Table 4). The management of pain and other symptoms is at the core of PC. Nevertheless, some symptoms (e.g. spasticity, fatigue) typically affect MS patients and were not addressed in clinical questions 4 and 5.

Patients with severe MS should be carefully, and regularly assessed in order to proactively detect their bio-psychosocial symptoms. Whenever necessary (e.g. in patients with severe cognitive compromise or communication problems), interviews with patient caregivers and use of proxy versions of symptom scales should be added to patient assessment.

Of 7195 records screened, 530 were assessed as full text and 44 (43 trials) were included. Ten studies addressed more than one symptom. The symptom with the highest number of studies was spasticity, followed by fatigue and pain (Table 4). Considering the type of intervention, 32/43 (75%) studies were on pharmacological interventions, 10/43 (23%) on non-pharmacological approaches, and 1/43 (2%) on a combination of pharmacological (botulinum toxin A) and physiotherapy interventions. Notably, we found no studies performed in this patient population on interventions targeted to the management of 10 out the 19 symptoms considered (Table 4). Recommendations on 4 symptoms (spasticity, fatigue, pain, and bladder problems) were produced. For each symptom, summary of finding tables are included in Appendix 6.

3.1 Spasticity

Spasticity is one of the most common symptoms in patients with severe MS, and its treatment includes anti-spastic drugs (oral or intrathecal), muscular injections with botulinum toxin A, exercise, electrical and magnetic stimulation, alone or in variable combinations.

The majority of the included papers on symptom management in severely affected MS patients (32/44 papers, 73%; 31 trials) addressed spasticity as an outcome [Baker 2007; Basmajian 1984; Basmajian 1986; Bass 1988; Collin 2010; Cutter 2000; Eyssette 1988; From 1975; Giovannelli 2007; Gusev 2008; Hoogstraten 1988; Hyman 2000; Killestein 2002; Lee 1993; Levine 1977; Marinelli 2015; Miller 2007; Mondrup 1984; Notcutt 2012; Novotna 2011; Penn 1989; Pompa 2017; Rinne 1980; Rudick 1987; Sachais 1977; Smolenski 1981; Snow 1990; Stien 1987; van Amerongen 2017; Vaney 2004; Zajicek 2003; Zajicek 2005]. Of these, 26 trials (84%) addressed drugs (baclofen, benzodiazepines, cannabinoids, gabaergics, tizanidine, and botulinum toxin) and 5 trials addressed

non-pharmacological treatments (exercise, radial shock wave therapy, and transcutaneous electrical nerve stimulation).

3.1.1 Pharmacological treatments of spasticity

Baclofen

Four randomized controlled trials (RCTs, 160 patients) were included, two comparing oral baclofen with placebo [Levine 1977, Sachais 1977], one comparing intrathecal baclofen with placebo [Penn 1989], and one comparing baclofen with diazepam [From 1975]. Six additional studies which compared tizanidine with oral baclofen are reported in the section on tizanidine. Doses and durations differed between these studies, which were published between 1975 and 1989.

Baclofen (oral) vs. placebo

Both RCTs (124 patients) reported a statistically significant difference for spasticity after 5 weeks in favor of baclofen, although in Levine 1977 (n=18, up to 45 mg/day) this was only shown for neurophysiological (EMG) measures, and not for clinical ratings. In Sachais 1977 (106 patients), baclofen up to 70-80 mg/day improved symptoms/signs of spasticity (flexor spams, pain, stiffness, resistance to passive joint movements, and tendon stretch reflexes) compared to placebo. Patient-based assessment of efficacy showed significant reductions in 3 symptoms (muscle spasms, clonus, and stiffness) and no difference for spasticity compared to placebo. No between-group differences were reported in Sachais 1977 on daily living activities (ADL) as assessed by clinicians (walking, sleeping, and general dexterity) or patients (daily activities, overall disability, and sexual activity).

No adverse events (AEs) were detected in Levine 1977. Somnolence (baclofen 60/85, 71%; placebo 29/81, 36%) and vertigo (baclofen 19/85, 22%; placebo 6/81, 7%) were the most common side effects in Sachais 1977. Side effects were generally mild and disappeared with continued therapy; no serious adverse events (SAE) was reported [Sachais 1977].

Baclofen (intrathecal) vs. placebo

Penn 1989 assessed the efficacy of 4-week intrathecal baclofen (62 to 749 µg/day) administered to MS patients (n=10, 9 of whom wheelchair-bound) or spinal cord trauma (n=10) who did not respond to oral baclofen. The study was a crossover RCT (one intrathecal administration of baclofen or placebo, followed by assessment on day 3) followed by an open trial on baclofen with

assessment every 6 months up to 26 months. A statistically significant reduction in Ashworth scale (AS) score (MS patients, $p<0.005$) and spasm frequency score (MS patients, $p<0.01$) was found for baclofen vs. placebo. During the open trial (continuous intrathecal baclofen administration), the improvement persisted. The following pump-related AEs were reported: 2 dislodged catheters, one pump failure (at 4 months), and one pump re-positioning due to occurrence of pain at the implantation site. No baclofen AEs (e.g. drowsiness) were detected. One MS patient died for complications that followed aspiration pneumonia 6 months after the pump was implanted.

Baclofen (oral) vs. diazepam

The study by From 1975 reported on 16 MS patients participating in a crossover RCT. No clear differences between baclofen (30 to 120 mg/day) and diazepam (10 to 40 mg/day) on various spasticity measures (AS, flexor spasms, clonus and walking ability) were shown. A significant difference in favor of baclofen was reported only for physician-based global assessment of efficacy ($p<0.001$). Concerning AEs, sedation was reported by 11/16 (69%) patients on diazepam vs. 5/16 (31%) patients on baclofen; there were no clear differences between groups for the other AEs.

Tizanidine

Six trials (378 patients) were included, all comparing tizanidine with baclofen [Bass 1988, Eyssette 1988, Hoogstraten 1988, Rinne 1980 (trial 3), Smolenski 1981, Stien 1987]. In addition, one sub-study compared tizanidine with placebo (Rinne 1980, trial 1) and one tizanidine with diazepam (Rinne 1980, trial 2). Doses and durations differed between studies with tizanidine administered between 2 and 32 mg/day for 5 to 10 weeks. Doses and durations differed between these studies, which were published between 1980 and 1988.

Tizanidine vs. placebo

Rinne 1980 trial 1 was a cross-over RCT on 32 participants (20 MS patients and 12 patients with chronic myelopathy) receiving tizanidine and matching placebo each for 4 weeks. A statistically significant difference in favor of tizanidine was reported, with 13/31 patients reporting improvement vs. 2/31 patients on placebo ($p<0.01$). The following AEs occurred more frequently in the tizanidine group compared to placebo group: drowsiness (17/32 vs. 11/32), and dry mouth (11/32 vs. 3/32). Overall tolerability was rated significantly worse in tizanidine compared to placebo ($p<0.05$).

Tizanidine vs. baclofen

All 6 trials (n=239) comparing tizanidine with baclofen for 4 to 8 weeks did not find clear differences between groups. AEs were assessed in all the studies. Somnolence, tiredness, fatigue or weakness were the most frequent AEs, reported in about 1/3 of patients, without a clear difference between groups. Rarely patients discontinued treatment due to intolerable side effects.

Tizanidine vs. diazepam

Rinne 1980 (trial 2) was a RCT on 30 MS patients comparing tizanidine with diazepam for 6 weeks. In both groups 9/15 patients (60%) reported improvement of spasticity symptoms. Moderate or bad tolerability was reported in 12/15 patients on diazepam (80%) vs. 5/15 patients on tizanidine (33%). Four patients (all on diazepam) withdrew from the study due to AEs.

Benzodiazepines

Four trials (102 patients) were included: 2 were double cross-over RCTs comparing oral diazepam with oral ketazolam or placebo [Basmajian 1984, Basmajian 1986]; one was a cross-over RCT comparing oral diazepam with oral baclofen [From 1975], and one (reported in the section on tizanidine) a RCT comparing oral diazepam with tizanidine [Rinne 1980, trial 2]. Doses and durations differed between studies, which were small and published between 1975 and 1986.

Diazepam vs. placebo

Two double cross-over RCTs on a mixed population (56 patients, 32 with MS and 24 with stroke) compared diazepam for two weeks (15 mg/day in week 1 and 30 mg/day in week 2) with placebo [Basmajian 1984, Basmajian 1986]. In both studies results on spasticity were not reported in a comprehensible way, and drowsiness, light-headedness, tiredness, and weakness were the most frequently reported AEs. Only Basmajian 1986 reported AEs: drowsiness occurred in 8/17 patients on diazepam (47%) vs. 4/17 patients on placebo (24%); light-headedness in 4/17 (24%) patients on diazepam vs. 0/17 patients on placebo. Two patients on diazepam withdrew from the study because of severe drowsiness.

Ketazolam vs. placebo

The same double cross-over RCTs compared diazepam for two weeks with placebo [Basmajian 1984, Basmajian 1986]. Results on spasticity were not reported in a comprehensible way. Considering AEs [Basmajian 1986], drowsiness was reported by 3/17 patients on ketazolam (18%) vs. 4/17 patients on placebo (24%); light-headedness by 5/17 patients on ketazolam (29%) vs. none on placebo. No study withdrawals were reported on ketazolam or on placebo.

Diazepam vs. ketazolam

The same double cross-over RCTs compared diazepam for two weeks with ketazolam [Basmajian 1984, Basmajian 1986]. Results on spasticity were not reported in a comprehensible way. Considering AEs [Basmajian 1986], drowsiness was reported by 47% diazepam vs. 18% ketazolam patients; light-headedness by 24% vs. 29%. Two patients on diazepam withdrew from the study (severe drowsiness) vs. none on ketazolam.

Diazepam vs. baclofen

One cross-over RCT [From 1975] on 16 MS patients reported no clear differences between 4-week diazepam (10 to 40 mg/day) and baclofen (30 to 120 mg/day). Various spasticity measures (AS, flexor spasms, clonus and walking ability) were assessed. Only for physician-based global assessment of efficacy, a significant difference was reported in favor of baclofen ($p<0.001$). Concerning AEs, sedation was reported more often for diazepam (11/16, 69%) compared to baclofen (5/16, 31%) with no clear differences between treatment groups for the other AEs.

Gabaergic drugs

Three crossover RCTs (70 patients) assessed the efficacy of gabapentin and progabide on spasticity compared to placebo.

Progabide vs. placebo

Rudick 1987 enrolled 32 MS patients receiving progabide up to 45 mg/kg/day or matching placebo over 4 weeks. Spasticity (AS score) significantly improved for progabide compared to placebo ($p<0.01$). Patients, physicians and study nurses all declared preference for progabide. In addition, weakness was not increased. Seven of the 32 patients (22%) stopped the study prematurely because of liver toxicity, which resolved after medication interruption.

Mondrup 1984 enrolled 16 patients (14 with MS, 2 with spinal cord disease) who received a lower dose of progabide (24.3 mg/kg/day) over 2 weeks. There was a reduction in spastic hypertonia ($p<0.01$), a suppression of patellar tendon reflexes ($p<0.01$), and a reduction in the frequency of flexor spasms ($p<0.05$) in the progabide group compared to placebo. No significant changes in voluntary power were reported. Global clinical impression favored progabide (vs. placebo) according to both patients (81%, 95% CI 54%–95%) and clinicians (87%, 95% CI 61%–98%). No AEs were reported.

Gabapentin vs. placebo

Cutter 2000 assessed a short course (6 days) of gabapentin (up to 1800 mg/day) in 22 MS patients. There was a statistically significant improvement in the gabapentin group vs. placebo on 4/5 patient-based measures: spasm severity scale, painful spasm scale, interference with function scale, and global assessment scale (no significant changes in spasm frequency scale); and on 2/4 clinician-based measures: Modified Ashworth scale (MAS) and plantar stimulation response (no significant changes in clonus scale and deep tendon reflexes scales). No AEs concerning fatigue and concentration and no laboratory abnormalities were reported.

L-Threonine

Lee 1993 assessed the efficacy of threonine (a precursor of the inhibitory neurotransmitter glycine) 6 g/day vs. placebo for 4 weeks, in a mixed patient population using a cross-over RCT with sequential design. The trial was terminated “in favor of l-threonine” after enrollment of 33 patients (21 of whom had severe MS). The results showed a modest reduction in spasticity (AS score) in the l-threonine group compared to placebo. Spasm scores were reduced with no clear differences between groups. Improvement was reported by 6/33 patients on l-threonine vs. 2/33 on placebo. Four patients dropped out (2 withdrew consent, 1 had infection during L-threonine, 1 had infection during washout period). AEs were minor, with 2 patients on l-threonine reporting indigestion (n=1) and diarrhea (n=1) which did not prevent them from completing the study. There was a consensus in the task force (TF) not to include a recommendation for l-threonine because of the very low quality of the evidence for this drug which is not used in clinical practice.

Cannabinoids

The efficacy of cannabinoids for MS spasticity was assessed in 7 trials (1371 patients), all published after 2000 that varied in size (16 to 667 patients), outcome measures and preparations.

D9-Tetrahydrocannabinol (THC) vs. placebo

In total, 3 parallel group RCTs (4 full-text papers) [van Amerongen 2017; Killestein 2002; Zajicek 2003; Zajicek 2005] assessed THC or cannabis in comparison to placebo for spasticity in MS patients.

In the study by van Amerongen, 24 MS patients were treated over 4 weeks. The primary endpoints were neurophysiological (H/M ratio) and objective measure of spasticity (AS). Spasticity was further assessed by a numeric rating scale (NRS) and a diary. There were no significant treatment effects on any of the spasticity outcome measures. Dizziness and headache were AEs reported slightly more often in the THC group. No SAE was reported. One patient assigned to placebo dropped out because of intolerable AEs.

Killestein 2002 compared THC, max 10 mg/day) or cannabis (max 10 mg/day) for 4 weeks to placebo in 16 MS patients, using a double crossover design. There were no significant effects of THC on spasticity (primary outcome measure) vs. placebo, assessed using the AS and a visual analogue scale (VAS). No SAEs were reported. Overall frequency of AEs was 20% in both groups.

The CAMS study [Zajicek 2003 and Zajicek 2005] was a multicenter 3-arm parallel RCT comparing THC (max 25 mg/day), cannabis (max 25 mg/daily), or placebo for 15 weeks. After 15 weeks of treatment, participants were offered to resume medication, for a maximum of 52 weeks. The study enrolled 667 MS patients. The primary endpoint was spasticity assessed with the AS, and the item on spasticity of an ad-hoc patient-reported symptom scale. There was a small treatment effect on the AS score at 12 months for THC and cannabis arms vs placebo (p=0.01; no THC vs placebo comparison available). Considering patient-based assessment, after 15 weeks improvement was reported in 89/176 (51%) THC-treated vs. 67/183 (37%) placebo-treated patients (p=0.008). Figures after 52 weeks were 47/142 (33%) vs. 27/156 (17%; p=0.001). The following AEs were reported more frequently in patients treated with THC than placebo at 15 weeks: dizziness/light headedness (63% THC vs. 22% placebo), dry mouth (28% vs. 8%), and

diarrhea (18% vs. 8%) [Zajicek 2003]. At one-year, dizziness/light headedness was reported by 15% (cannabinoids) vs. 4% (placebo). Nine out of 417 patients were lost to follow-up (7 for intolerable side-effects) in the cannabinoids groups and 6/213 patients in the placebo group. There were 6 deaths during follow-up (3 from pneumonia, one each from carcinoma of the cervix, seizure, and ischaemic heart disease) [Zajicek 2005]. A further patient (THC group) died in week 42 from urinary and respiratory infections contracted during week 12. Neither death was considered to be related to the study medication. Overall, there were no major safety concerns.

Cannabis sativa plant extract vs. placebo

In total, 4 papers (3 trials) compared cannabis sativa plant extract to placebo for spasticity in patients with MS [Killestein 2002; Vaney 2004; Zajicek 2003 and Zajicek 2005].

In the Killestein 2002 study reported above there were no significant effects of cannabis treatment on spasticity (AS, VAS). AEs were more frequent (41%) during cannabis treatment compared with placebo treatment (20%; p=0.01). Notably, spasticity was also reported as an AE in 5/16 (31%) of the cannabis group patients vs. 3/16 (19%) of the placebo group patients. One SAE was reported in the cannabis group, consisting of acute (5-hour) psychosis.

Vaney 2004 compared cannabis (max 30 mg daily for 14 days) to placebo in a crossover RCT in 50 MS patients. There was no significant difference in spasticity (primary outcome) on the AS score between groups. No SAE occurred during the trial. There were 6 dropouts in the cannabis group vs. one in the placebo group. AEs were slightly more frequent and more severe during cannabis treatment, and toxicity symptoms, which were generally mild, were more pronounced during cannabis treatment. No clinically relevant changes were observed in physical examinations or in any hematology or biochemistry parameter.

In the CAMS study reported above [Zajicek 2003 and Zajicek 2005] there was a small treatment effect on the AS score at 12 months for THC and cannabis arms vs placebo (p=0.01; no cannabis vs placebo comparison available). Considering patient-based assessment, after 15 weeks improvement in spasticity (ad hoc patient-reported scale) was found in 95/184 (52%) cannabis-treated patients vs. 67/183 (37%) placebo-treated patients (p=0.004). Figures after 52 weeks were 45/156 (29%) vs. 27/156 (17%; p=0.02). The following AEs were reported more frequently in patients treated with cannabis than placebo at 15 weeks: dizziness/light headedness (54% cannabis vs. 22% placebo), dry mouth (22% vs. 8%), and diarrhea (19% vs. 8%) [Zajicek 2003]. At

one-year, dizziness/light headedness was reported by 19% (cannabis) vs. 4% (placebo). Overall, there were no major safety concerns.

Cannabinoids vs. other cannabinoids

Cannabinoids were compared to other cannabinoids for spasticity in MS patients in two RCTs (3 papers) [Killestein 2005; Zajicek 2003 and Zajicek 2005].

Killestein 2002 did not find any difference on spasticity (AS and VAS) between THC (max 10 mg/day) and cannabis (max 10 mg/day) administered for 4 weeks in the double crossover RCT reported above. The occurrence of AEs was higher during cannabis (41%) than THC treatment (20%). One SAE was reported in the cannabis group, consisting of acute (5-hour) psychosis.

In the CAMS study reported above [Zajicek 2003 and Zajicek 2005], THC (max 25 mg/day) was compared to cannabis (max 25 mg/day). No direct comparison between THC and cannabis was reported on the AS. Similar improvements were rated by patients after 15 weeks and 12 months with no differences between THC and cannabis. No difference in AEs was found between the two cannabinoids.

Nabiximols vs. placebo

Collin 2010 compared nabiximols (1:1 mix of THC and cannabidiol extracted from cloned cannabis sativa, available as an oromucosal spray; 2.7 mg THC and 2.5 mg cannabidiol [CBD], up to 24 sprays/24 h) to placebo over 15 weeks in 337 MS patients. The primary endpoint was patient-based NRS of spasticity (see meta-analysis below). In addition, no differences between groups were found for the MAS score. A total of 55 patients (16%) discontinued treatment early: 35 (21%) in the nabiximols group and 20 (12%) in the placebo group. Of these 55 patients, 32 (58%) withdrew from the study. The primary reason given for withdrawal was AE occurrence: 9 patients (5%) on nabiximols and 5 (3%) on placebo. The following AEs were reported more frequently in the nabiximols group compared to placebo: dizziness (53/167 [32%] vs. 17/170 [10%]), fatigue (42/167 [25%] vs. 32/170 [19%]), somnolence (24/167 [14%] vs. 7/170 [4%]), nausea (53/167 [32%] vs. 17/170 [10%]), asthenia (26/167 [16%] vs. 11/170 [6%]) and vertigo (19/167 [11%] vs. 7/170 [4%]). Two subjects died from cancer during the study: neither death was considered to be related to the (active) study medication.

Novotna 2011 compared add-on nabiximols (2.7 mg THC and 2.5 mg CBD, up to 12 sprays/24 h) to placebo in 241 MS patients over 12 weeks. The RCT had an enriched study design in which

responders to nabiximols (patients improving ≥ 20% on patient-reported NRS spasticity) were identified in a 4-week single-blind phase. The 241/572 responder patients participated in a double-blind RCT, reported here. Results for NRS spasticity (primary outcome measure) and caregiver global impression of change (CGIC) concerning "ease of transfer" are reported below. No differences between groups were found for the MAS score. Seventeen patients discontinued the treatment early (7%): 15 were on nabiximols (4 due to AEs, 11 due to withdrawal of consent). AEs were overall few and similar between nabiximols and placebo, with no single event occurring at a rate >10% in either group; the most common AEs were vertigo (6% nabiximols vs. 1% placebo), and fatigue (5% vs. 1%).

Notcutt 2012 compared nabiximols (mean 7.7 sprays daily) to placebo in 36 MS patients over 5 weeks in a parallel-group withdrawal RCT. The primary endpoint was spasticity (NRS; see below). MS patients with ongoing benefit from nabiximols for at least 3 months were randomized to nabiximols or placebo after a screening period of one week. No differences between groups were found for the MAS score. There was one SAE (pain in hip and thigh and lumbar spinal stenosis) in a patient on nabiximols, which was considered unrelated to study medication. The only AE reported in association with abnormal laboratory values was a mild increase in gamma-glutamyl transferase in one patient on nabiximols.

Figure 4 shows the results ('forest plots') of a meta-analysis performed of the two outcome measures that were used in all the 3 RCTs [Collin 2010, Novotna 2011, Notcutt 2012]: patient-reported NRS spasticity, and CGIC "ease of transfer". Mean NRS spasticity difference favored nabiximols (-0.51; 95% CI -0.96 to -0.07); and the odds ratio (OR) for CGIC "ease of transfer" improvement was 1.99 (95% CI 1.17 to 3.38) for nabiximols vs. placebo.

Botulinum toxin A

Three RCTs (189 patients) reported on the use of botulinum toxin A (BTA) to treat hip adductor muscles spasticity in MS patients vs. placebo. The largest RCT [Gusev 2008] enrolled 106 patients who received BTA 1000 to 1500 units (depending on the individual clinical status) and showed no difference between BTA and placebo on spasticity outcomes and functioning at 12 weeks. Asthenia was the most frequent AE (22%, BTA group; 6%, placebo) which was however mild.

In the 4-arm RCT study by Hyman 2000, 74 MS patients were studied for 12 weeks after a single administration of BTA 500 units, 1000 units, 1500 units, or placebo. The primary endpoint of passive hip abduction measured at week 4 did improve in all groups vs. placebo, but with no

differences between groups. The maximum distance between knees (co-primary endpoint) improved significantly in the 1500 units group vs. placebo (p=0.02). All other outcome measures showed improvements, with no significant differences between-groups. There were 14 drop outs (19%). AEs were reported by 32/58 (55%) patients in the BTA vs. 10/16 (63%) patients in the placebo group. Compared with the two lower dose groups, twice as many AEs were reported by the 1500 unit group (2.7/patient). The incidence of muscle weakness was higher for the 1500 unit group (36%) compared to placebo (6%).

Snow 1990, in a crossover RCT, treated 9 MS patients with BTA 400 units showing a significant reduction in clinician-based assessment of spasticity in the BTA group compared to placebo (p=0.009) after 6 weeks. No SAEs attributable to BTA were reported.

3.1.2 Non-pharmacological treatment of spasticity

Exercise

Three trials (89 patients) evaluated exercise interventions for spasticity [Baker 2007; Giovannelli 2007, and Pompa 2017].

Baker 2007 tested the use of a standing frame (30 min/day for 3 weeks) compared to daily exercise in 6 MS patients, using a crossover design. The primary outcome measure was spasticity (AS). No significant differences were found between groups for spasticity, although a downward trend was seen in the AS scores for knee flexion and ankle dorsiflexion with standing. AEs were not reported.

Giovannelli 2007 enrolled 40 MS patients in a RCT comparing physiotherapy (40 min/d for 15 days) after the BTA injection to BTA only, over 12 weeks. There was no primary endpoint. Spasticity was assessed with the MAS and a VAS. There was a significant decrease of spasticity in the BTA and physiotherapy added-on group after 2 weeks (MAS; p<0.01), 4 weeks (MAS and VAS; p<0.01), and 12 weeks (MAS and VAS; p<0.01) compared to the BTA group. The MAS mean change (SD) from baseline to week 12 was -0.95 (0.78) in the BTA and physiotherapy added-on group vs. -0.28 (0.46) in the BTA toxin group (p<0.01).

Pompa 2017 enrolled 43 MS patients who received robot-assisted gait training (RAGT, 12 sessions over 4 weeks) added on an in-patient rehabilitation programme. The primary outcomes were walking capacity and walking ability, while (lower limb) spasticity was one of the secondary outcomes (VAS) assessed in a subgroup of participants (n=10, RAGT group; 15, control group).

There was a statistically significant reduction in spasticity in the RAGT group in comparison to controls (p=0.048) at 4 weeks. The RAGT group improved from 5.05 (1.01) to 3.40 (1.24) (p=0.007). No AEs were reported.

Radial shock wave therapy (RSWT)

Marinelli 2015 compared RSWT (BTL-6000 SWT Topline Unit, BTL, Italy; 1/week for 4 sessions) to placebo in 34 MS patients over 8 weeks. The primary outcome of the study was pain. Spasticity was assessed with the Medical Research Council (MRC) muscle strength scale, and the MAS. After RSWT, MAS score significantly decreased only at 4 weeks, while there were no significant changes for muscle strength (MRC). No between-group differences were found. AEs were not observed.

There was a consensus in the task force not to include a recommendation for RSWT because spasticity was a secondary outcome and no effect was found.

Transcutaneous electrical nerve stimulation (TENS)

Miller 2007 compared TENS (8 hours) to TENS (1 hour) for spasticity in 32 MS patients. Lower limb spasticity was assessed as the primary outcome using the Global Spasticity Score (GSS). After both application times of TENS, there were no significant reductions in the GSS. AEs were not reported.

References

van Amerongen G, Kanhai K, Baakman AC, et al. Effects on spasticity and neuropathic pain of an oral formulation of delta9-tetrahydrocannabinol in patients with progressive multiple sclerosis. Clin Ther 2018; 40: 1467-1482.

Baker K, Cassidy E, Rone-Adams S. Therapeutic standing for people with multiple sclerosis: efficacy and feasibility. International Journal of Therapy and Rehabilitation 2007; 14: 104-109.

Basmajian JV, Shankardass K, Russell D, Yucel V. Ketazolam treatment for spasticity: double-blind study of a new drug. Arch Phys Med Rehabil 1984; 65: 698-701.

Basmajian JV, Shankardass K, Russell D. Ketazolam once daily for spasticity: double-blind cross-over study. Arch Phys Med Rehabil 1986; 67: 556-557.

Bass B, Weinshenker B, Rice GP, et al. Tizanidine versus baclofen in the treatment of spasticity in patients with multiple sclerosis. Can J Neurol Sci 1988; 15: 15-19.

Collin C, Ehler E, Waberzinek G, et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurol Res 2010; 32: 451-459.

Cutter NC, Scott DD, Johnson JC, Whiteneck G. Gabapentin effect on spasticity in multiple sclerosis: a placebo-controlled, randomized trial. Arch Phys Med Rehabil 2000; 81: 164-169.

Eyssette M, Rohmer F, Serratrice G, Warter JM, Boisson D. Multi-centre, double-blind trial of a novel antispastic agent, tizanidine, in spasticity associated with multiple sclerosis. Curr Med Res Opin 1988; 10: 699-708.

From A, Heltberg A. A double-blind trial with baclofen (Lioresal) and diazepam in spasticity due to multiple sclerosis. Acta Neurol Scand 1975; 51: 158-166.

Giovannelli M, Borriello G, Castri P, Prosperini L, Pozzilli C. Early physiotherapy after injection of botulinum toxin increases the beneficial effects on spasticity in patients with multiple sclerosis. Clin Rehabil 2007; 21: 331-337.

Gusev YI, Banac M, Simonow A, et al. Efficacy and safety of botulinum type a toxin in adductor spasticity due to multiple sclerosis. J Musculoskeletal Pain 2008; 16: 175-88.

Hoogstraten MC, van der Ploeg RJ, vd Burg W, Vreeling A, van Marle S, Minderhoud JM. Tizanidine versus baclofen in the treatment of spasticity in multiple sclerosis patients. Acta Neurol Scand 1988; 77: 224-230.

Hyman N, Barnes M, Bhakta B, et al. Botulinum toxin (Dysportt) treatment of hip adductor spasticity in multiple sclerosis: a prospective, randomised, double blind, placebo controlled, dose ranging study. J Neurol Neurosurg Psychiatry 2000; 68: 707-712.

Killestein J, Hoogervorst EL, Reif M, et al. Safety, tolerability, and efficacy of orally administered cannabinoids in MS. Neurology 2002; 58: 1404-1407.

Lee A, Patterson V. A double-blind study of L-threonine in patients with spinal spasticity A double-blind study of L-threonine in patients with spinal spasticity. Acta Neurol Scand 1993; 88: 334-338.

Levine IM, Jossmann PB, DeAngelis V. Lioreseal, a new muscle relaxant in the treatment of spasticity--a double-blind quantitative evaluation. Dis Nerv Syst 1977; 38: 1011-1015.

Marinelli L, Mori L, Solaro C, et al. Effect of radial shock wave therapy on pain and muscle hypertonia: a double-blind study in patients with multiple sclerosis. Mult Scler 2015; 21: 622-629.

Miller L, Mattison P, Paul L, Wood L. The effects of transcutaneous electrical nerve stimulation (TENS) on spasticity in multiple sclerosis. Mult Scler 2007; 13: 527-533.

Mondrup K, Pedersen E. The clinical effect of the GABA-agonist, progabide, on spasticity. Acta Neurol Scand 1984; 69: 200-206.

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; 18: 219-228.

Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. Eur J Neurol 2011; 18: 1122-31.

Penn RD, Savoy SM, Orcos D, et al. Intrathecal baclofen for severe spinal spasticity. N Engl J Med 1989; 320: 1517-1521.

Pompa A, Morone G, Iosa M, et al. Does robot-assisted gait training improve ambulation in highly disabled multiple sclerosis people? A pilot randomized control trial. Mult Scler 2017; 23: 696-703.

Rinne UK. Tizanidine treatment of spasticity in multiple sclerosis and chronic myelopathy. Therapeutic Research 1980; 28 827-836.

Rudick RA, Breton D, Krall RL. The GABA-agonist progabide for spasticity in multiple sclerosis. Arch Neurol 1987; 44: 1033-1036.

Sachais BA, Legue JN, Carey MS. Baclofen, a new antispastic drug. A controlled, multicenter trial in patients with multiple sclerosis. Arch Neurol 1977; 34: 422-428.

Smolenski C, Muff S, Smolenski-Kautz S. A double-blind comparative trial of new muscle relaxant, tizanidine (DS 103-282), and baclofen in the treatment of chronic spasticity in multiple sclerosis. Curr Med Res Opin 1981; 7: 374-383.

Snow BJ, Tsui JKC, Bhatt M, Varelas M, Hashimoto SA, Calne DB. Treatment of spasticity with botulinum toxin: a double-blind study. Ann Neurol 1990; 28: 512-515.

Stien R, Nordal HJ, Oftedal SI, Slettebø M. The treatment of spasticity in multiple sclerosis: a double-blind clinical trial of a new anti-spastic drug tizanidine compared with baclofen. Acta Neurol Scand 1987; 75: 190-194.

Vaney C, Heinzel-Gutenbrunner M, Jobin P, et al. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis:

A randomized, double-blind, placebo-controlled, crossover study. Mult Scler 2004; 10(4): 417-424.

Zajicek J, Fox P, Sanders H, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet 2003; 362: 1517-1526.

Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry 2005; 76: 1664-1669.

3.2 Fatigue

In total, 10/44 publications (9 trials) on symptomatic treatments addressed fatigue as an outcome. Five of these publications (4 trials) were on drugs (cannabinoids and 4-Aminopyridine) [Collin 2010; Rossini 2001; van Amerongen 2017; Zajicek 2003; Zajicek 2005] and 5 publications on exercise [Klefbeck 2003; Pompa 2017; Rice 2015; Skjerbaek 2014; Straudi 2015].

3.2.1 Pharmacological treatment for fatigue

Cannabinoids

D9-Tetrahydrocannabinol (THC) or cannabis sativa plant extract (cannabis) vs. placebo

In total, 2 parallel group RCTs (3 full-text papers) [van Amerongen 2017; Zajicek 2003; Zajicek 2005] evaluated THC or cannabis in comparison to placebo.

In the study by van Amerongen, 24 MS patients were treated with THC (16 mg/daily) over 4 weeks. The primary endpoints were neurophysiological (H/M ratio) and objective measure of spasticity (AS), while fatigue was assessed as one of the secondary outcomes (Fatigue Severity Scale, FSS). There was a significant reduction in fatigue after 2 weeks of treatment compared to placebo, but the difference was not significant over 4 weeks. As AEs, dizziness and headache appeared slightly more often in the THC group, while no SAEs were reported. One patient (assigned to placebo) dropped out because of intolerable AEs.

The CAMS study [Zajicek 2003 and Zajicek 2005] was a multicenter 3-arm parallel RCT comparing THC (up to 25 mg/daily for 15 weeks), cannabis (up to 25 mg/daily for 15 weeks), or placebo. After 15 weeks of treatment, participants were offered to resume medication, for a maximum of 52 weeks. The study enrolled 667 MS patients. The primary endpoint was spasticity. Fatigue was addressed with two items on energy levels and tiredness. There was no significant improvement on both items at 15 weeks [Zajicek 2003]. At 52 weeks improvement on energy levels was not significant, while tiredness improved in 58/254 (23%) of cannabinoids-treated patients vs. 17/148 (11%) of placebo-treated patients (p=0.005) [Zajicek 2005]. The following AEs were reported more frequently in patients treated with cannabinoids than placebo at 15 weeks: dizziness/light headedness (58% cannabinoids vs. 22% placebo), dry mouth (29% vs. 8%), and diarrhea (19% vs. 8%) [Zajicek 2003]. At one-year dizziness/light headedness was reported by 17% (cannabinoids) vs. 4% (placebo). Nine out of 417 patients were lost to follow-up (7 for intolerable side-effects) in the cannabinoids groups and 6/213 patients in the placebo group. There were six deaths during the

follow up phase (3 from pneumonia, one each from carcinoma of the cervix, seizure, and ischaemic heart disease) [Zajicek 2005]. A further patient (THC group) died in week 42 from urinary and respiratory infections contracted during week 12. Overall, there were no major safety concerns.

Nabiximols

In a RCT, Collin 2010 compared nabiximols (1:1 mix of THC and cannabidiol extracted from cloned cannabis sativa, available as an oromucosal spray; 2.7 mg THC and 2.5 mg CBD, up to 24 sprays in 24 hours) to placebo over 15 weeks in 337 MS patients. While the primary endpoint was the effect on spasticity, fatigue was addressed together with other symptoms on a 0-10 NRS. There were no differences between groups for fatigue. Notably, fatigue was also reported as an AE in 42/167 (25%) of the nabiximols group patients vs. 32/170 [19%) of the placebo group patients. A total of 55 subjects (16%) discontinued treatment early: 35 (21%) in the nabiximols group and 20 (12%) in the placebo group (p=0.02). Of these 55 subjects, 32 (58%) withdrew from the study. The primary reason given for withdrawal was AE occurrence: 9 subjects (5%) on active treatment and 5 (3%) on placebo. Besides fatigue, the following AEs were reported more frequently in the nabiximols group compared to placebo: dizziness (53/167 [32%] vs.17/170 [10%]), somnolence (24/167 [14%] vs. 7/170 [4%]), nausea (53/167 [32%] vs.17/170 [10%]), asthenia (26/167 [16%] vs. 11/170 [6%]) and vertigo (19/167 [11%] vs.7/170 [4%]). Two subjects died from cancer during the study: neither death was considered to be related to the (active) study medication.

Aminopyridine

Rossini 2001 performed a crossover RCT with 54 MS patients treated with placebo and 4-Aminopyridine (4-AP, 32 mg per day), each for 6 months. The primary outcome was fatigue (FSS). After 6 months both groups improved, but improvement did not significantly differ between groups (p=0.19). In total, 11 patients (9 in 4-AP, 2 in the placebo group) complained of transient side-effects consisting of paresthesia, abdominal pain, vertigo, anxiety, pollachiuria, and tachycardia at the beginning of the treatment, which gradually disappeared.

3.2.2 Exercise treatment for fatigue

Robot-assisted gait training

Two RCTs [Straudi 2016, Pompa 2017] compared robot-assisted gait training to conventional gait training in patients with MS.

Straudi 2016 enrolled 52 MS outpatients who received 12 sessions over 6 weeks. While primary outcomes were gait speed and endurance improvements, fatigue was one of the secondary outcomes (FSS). No significant effects on the FSS were found. No adverse events were reported.

Pompa 2017 enrolled 43 MS patients who received 12 sessions over 4 weeks added on an in-patient rehabilitation programme. The primary outcomes were walking capacity and walking ability, while fatigue was one of the secondary outcomes (FSS). There was a significant difference in the FSS in favor of the robot-assisted gait training ($p=0.013$). No AEs were reported.

Other training

Three RCTs [Klefbeck 2003, Rice 2015, and Skjerbaek 2014] assessed the efficacy of other trainings (i.e. inspiratory muscle training, upper body endurance training, manual wheelchair propulsion training).

Klefbeck 2003 compared 10 weeks of outpatient supervised inspiratory muscle training to deep-breathing exercises as part of their ordinary physical training in 15 MS patients. Fatigue (FSS) was one of the secondary outcome measures, and there was no difference between groups. AEs were not reported by the authors.

Rice 2015 compared a community-based propulsion training program of custom-fit, ultralight manual wheelchairs against no training in 14 MS patients followed for 3 months. Several outcome measures were investigated, including fatigue (FSS). There was a trend towards reduced fatigue in patients receiving the training ($p=0.068$). AEs were not reported by the authors.

Skjerbaek 2014 tested standard individualized MS rehabilitation plus 10 sessions of upper-body endurance training against standard individualized MS rehabilitation in 11 MS inpatients over 4 weeks. Fatigue (one of the tertiary outcome measures) was assessed with the Fatigue Scale for Motor and Cognitive functions. No significant group differences were seen for this outcome. One patient dropped out of the intervention group and no adverse events were reported.

References

van Amerongen G, Kanhai K, Baakman AC, et al. Effects on spasticity and neuropathic pain of an oral formulation of delta9-tetrahydrocannabinol in patients with progressive multiple sclerosis. Clin Ther 2018; 40: 1467-1482.

Collin C, Ehler E, Waberzinek G, et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurol Res 2010; 32: 451-459.

Klefbeck B, Hamrah Nedjad J. Effect of inspiratory muscle training in patients with multiple sclerosis. Arch Phys Med Rehabil 2003; 84: 994-999.

Pompa A, Morone G, Iosa M, et al. Does robot-assisted gait training improve ambulation in highly disabled multiple sclerosis people? A pilot randomized control trial. Mult Scler 2017; 23: 696-703.

Rice IM, Rice LA, Motl RW. Promoting physical activity through a manual wheelchair propulsion intervention in persons with multiple sclerosis. Arch Phys Med Rehabil 2015; 96: 1850-1858.

Rossini PM, Pasqualetti P, Pozzilli C, et al. Fatigue in progressive multiple sclerosis: results of a randomized, double-blind, placebo-controlled, crossover trial of oral 4-aminopyridine. Mult Scler 2001; 7: 354-358.

Skjerbæk AG, Næsby M, Lützen K, et al. Endurance training is feasible in severely disabled patients with progressive multiple sclerosis. Mult Scler 2014; 20: 627-630.

Straudi S, Fanciullacci C, Martinuzzi C, et al. The effects of robot-assisted gait training in progressive multiple sclerosis: a randomized controlled trial. Mult Scler 2016; 22: 373-384.

Zajicek J, Fox P, Sanders H, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet 2003; 362: 1517-1526.

Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry 2005; 76: 1664-1669.

3.3 Pain

Seven papers (6 trials) [Collin 2010, Marinelli 2015; Miller 2007; Rog 2005; van Amerongen 2017; Zajicek 2003; Zajicek 2005] of the 44 included papers on symptomatic treatments in patients with MS addressed pain as an outcome. Of these, 4 trials were on drugs (cannabinoids) and 2 on non-pharmacological treatment options.

3.3.1 Pharmacological treatment for pain

Cannabinoids

D9-Tetrahydrocannabinol (THC) or cannabis sativa plant extract (cannabis) vs. placebo

In total, 2 parallel group RCTs (3 full-text papers) [van Amerongen 2017; Zajicek 2003; Zajicek 2005] evaluated THC or cannabis in comparison to placebo for pain.

In the study by van Amerongen, 24 MS patients were treated with THC (16 mg/daily) over 4 weeks). The primary endpoints were neurophysiological (H/M ratio) and objective measure of spasticity (AS), while pain was assessed using a NRS and patient diaries. Pain was significantly reduced after 2 weeks, but not after 4 weeks and when reported in the daily diaries. A subgroup analysis was performed in participants who experienced subjective pain (n=17) at the start of treatment, showing a significant reduction in pain at 2 and 4 weeks. As AEs, dizziness and headache were reported slightly more often in the THC group, while no SAEs were reported. One patient (assigned to placebo) dropped out because of intolerable AEs.

The CAMS study [Zajicek 2003 and Zajicek 2005] was a multicenter 3-arm parallel RCT comparing THC (up to 25 mg/daily for 15 weeks), cannabis (up to 25 mg/daily for 15 weeks), or placebo. After 15 weeks of treatment, participants were offered to resume medication, for a maximum of 52 weeks. The study enrolled 667 MS patients. The primary endpoint was spasticity. Pain was addressed with one item. After 15 weeks improvement was reported in 132/277 (48%) cannabinoids-treated patients vs. 42/142 (30%) placebo-treated patients ($p < 0.0001$). Figures after 52 weeks were 68/231 (29%) vs. 17/125 (14%; $p=0.001$). The following AEs were reported more frequently in patients treated with cannabinoids than placebo at 15 weeks: dizziness/light headedness (58% cannabinoids vs. 22% placebo), dry mouth (29% vs. 8%), and diarrhea (19% vs. 8%) [Zajicek 2003]. At one-year dizziness/light headedness was reported by 17% (cannabinoids) vs. 4% (placebo) and pain was also reported as an AE in 23% (cannabinoids) vs. 17% (placebo). The higher occurrence of pain in the cannabinoids groups was found for cannabis (26%) while for THC it occurred in 19% of the patients (vs. 17% in placebo group) [Zajicek 2005]. Nine out of 417

patients were lost to follow-up (7 for intolerable side-effects) in the cannabinoids groups and 6/213 patients in the placebo group. There were 6 deaths during the follow up phase (3 from pneumonia, one each from carcinoma of the cervix, seizure, and ischaemic heart disease) [Zajicek 2005]. A further patient (THC group) died in week 42 from urinary and respiratory infections contracted in week 12. Neither death was considered to be related to the (active) study medication. Overall, there were no major safety concerns.

Nabiximols vs. placebo

Two parallel group RCTs (2 full-text papers) evaluated nabiximols (1:1 mix of THC and cannabidiol extracted from cloned Cannabis sativa, available as an oromucosal spray) vs. placebo for pain [Collin 2010 and Rog 2005].

Collin 2010 compared nabiximols (2.7 mg THC and 2.5 mg CBD, up to 24 sprays in 24 hours) to placebo over 15 weeks in 337 MS patients. While the primary endpoint was the effect on spasticity, pain was addressed together with other symptoms on a 0-10 NRS. There were no differences between groups on pain. A total of 55 subjects (16%) discontinued treatment early: 35 (21%) in the nabiximols group and 20 (12%) in the placebo group. Of these 55 subjects, 32 (58%) withdrew from the study. The primary reason given for withdrawal was AEs in 9 subjects (5%) on nabiximols and 5 (3%) on placebo. The following AEs were reported more frequently in the nabiximols group compared to placebo: dizziness (53/167 [32%] vs. 17/170 [10%]), fatigue (42/167 [25%] vs. 32/170 [19%]), somnolence (24/167 [14%] vs. 7/170 [4%]), nausea (53/167 [32%] vs. 17/170 [10%]), asthenia (26/167 [16%] vs. 11/170 [6%]) and vertigo (19/167 [11%] vs. 7/170 [4%]). Two subjects died from cancer during the study: neither death was considered to be related to the (active) study medication.

Rog 2005 compared nabiximols (2.7 mg THC and 2.5 mg CBD, up to 48 sprays in 24 hours) to placebo in 66 patients with MS and central pain over 5 weeks (1-week run-in, 4-week treatment). Pain was assessed with an 11-point NRS. After 5 weeks, nabiximols (mean NRS change -2.7, 95% CI -3.4 to -2.0) was superior to placebo (mean NRS change –1.4 95% CI -2.0 to -0.8 $p < 0.005$) in reducing intensity of pain.

Nabiximols was generally well tolerated, although more patients on the drug reported dizziness (nabiximols 18/34 vs. placebo 5/32), dry mouth (4/34 vs. 0/32), and somnolence (3/34 vs. 0/32). Two patients withdrew, both on nabiximols. One developed an AE (agitation with tachycardia and hypertension after 4 sprays) which settled with conservative management within 3 hours. She

declined further study medication and withdrew 7 days later. The second patient developed paranoid ideation and was withdrawn from study medication at the investigator's discretion in the second treatment week.

3.3.2 Non-pharmacological treatment of pain

Radial shock wave therapy (RSWT)

Marinelli 2015 compared RSWT (BTL-6000 SWT Topline Unit, BTL, Italy; 1/week for 4 sessions) to placebo in 34 patients with MS over 8 weeks, and pain (VAS) was the primary outcome. After RSWT, pain significantly decreased at all follow-up visits, with a maximal effect one week after the last (4-week) session. This effect was already disclosed one week after the first session and persisted 4 weeks after the last session. There was no difference between groups.

Transcutaneous Electrical Nerve Stimulator (TENS)

Miller 2007 compared TENS (8 hours) to TENS (1 hour) for spasticity in 32 MS patients. Pain (VAS) was one of the secondary outcomes. The 8-hour application time led to significant reductions of pain (p=0.008) compared to the 1-hour application.

References

van Amerongen G, Kanhai K, Baakman AC, et al. Effects on spasticity and neuropathic pain of an oral formulation of delta9-tetrahydrocannabinol in patients with progressive multiple sclerosis. Clin Ther 2018; 40: 1467-1482.

Collin C, Ehler E, Waberzinek G, et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurol Res 2010; 32: 451-459.

Marinelli L, Mori L, Solaro C, et al. Effect of radial shock wave therapy on pain and muscle hypertonia: a double-blind study in patients with multiple sclerosis. Mult Scler 2015; 21: 622-629.

Miller L, Mattison P, Paul L, Wood L. The effects of transcutaneous electrical nerve stimulation (TENS) on spasticity in multiple sclerosis. Mult Scler 2007; 13: 527-533.

Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005; 65: 812–819.

Zajicek J, Fox P, Sanders H, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet 2003; 362: 1517-1526.

Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry 2005; 76: 1664-1669.

3.4 Bladder symptoms

Bladder symptoms are present in over 90% of patients with progressive MS. Difficulty with storage control (urinary frequency, urgency, and incontinence) are the most common symptoms, caused by neurogenic detrusor overactivity. Approximately half of the patients have coexistent voiding difficulty due to detrusor-sphincter-dyssynergia [Phè 2016].

Six of the 44 included papers (4 trials) on symptom management in severely affected MS patients addressed drugs to improve urinary continence [Valiquette 1996, Fader 2007, Collin 2010, Zajicek 2003, Zajicek 2005, Freeman 2006]. Two studies were crossover RCTs: one compared antimuscarinics for urinary incontinence [Fader 2007] and one desmopressin intranasal spray to placebo for nocturia [Valiquette 1996]. Two studies were RCTs on cannabinoids which included urinary symptoms as secondary outcomes [Collin 2010, Zajicek 2003, Zajicek 2005, Freeman 2006].

Atropine (intravesical) vs. oxybutinine

The study by Fader 2007 compared intravesical atropine (up to 24 mg/day) to oxybutinine immediate release (up to 5 mg 4 times/day) for 2 weeks, using a crossover design. Of 64 randomized patients, 57 completed both study periods and were analyzed. The primary outcome measure was bladder capacity, defined as average recorded voided volume (spontaneous, catheterized or combined if a spontaneous void was followed immediately by a catheterized void). Secondary outcome measures were average 24h voiding frequency, incontinence events, and 2 patient reported outcomes (the King's Health Questionnaire, and an ad-hoc 12-item side effect rating questionnaire). Change in bladder capacity after 2 weeks was higher, but of borderline statistical significance, in the atropine arm vs. oxybutinine arm (mean between-arm difference 24.1 ml; 95% CI 0.4-49.7; p=0.053). Changes in secondary efficacy measures were similar between study arms. In terms of AEs, one patient felt dizzy and faint immediately after the test dose of atropine given during screening and was excluded from the study; 7 patients reported urinary retention (6 on atropine, one on oxybutynin). Dry mouth and the other patient-reported side effects (ad hoc side effect rating questionnaire) were significantly better in the atropine group.

In terms of acceptability of the intravesical atropine injection procedure, most of the patients (47/57, 82%) reported that it required ≤ 5 minutes more per catheterization, 6 between 5-10 minutes, and 4 (7%) >10 minutes. Overall 34/57 patients (63%) found the procedure easy, although 3 (5%) found it difficult.

Cannabinoids

The efficacy of cannabinoids for urinary symptoms (secondary outcome measures) was assessed in 3 trials (1004 patients).

D9-Tetrahydrocannabinol (THC) vs. placebo

The CAMS study [Zajicek 2003, Zajicek 2005, Freeman 2006] was a multicenter 3-arm parallel RCT comparing THC (max 25 mg/day), cannabis (max 25 mg/daily), or placebo for 15 weeks. After 15 weeks of treatment, participants were offered to resume medication, for a maximum of 52 weeks. The study enrolled 667 MS patients. The primary endpoint was spasticity. All patients were assessed for urge incontinence episodes, except for those with a permanent catheter (108/657, 16%) [Freeman 2006]. At baseline and at week 13 patients completed a 3-day diary recording the number of urinary incontinence episodes (primary outcome of this exploratory sub-study [Freeman 2006]) and the King's Health Questionnaire; the physician asked specific questions about 'bladder problems' and 'incontinence' within the United Kingdom Neurological Disability Score (UKNDS). In addition, one of the 4 questions on the overall effect of treatment at 15 weeks, was on bladder function.

The number of urge incontinence episodes showed a 19% reduction in the THC group vs. placebo (p=0.04). Patients reporting overall improvement in bladder function were 40% for THC vs. 33% for placebo. There were no significant differences in any of the King's Health Questionnaire domains.

Six patients died during the follow up phase of the CAMS study: 3 of pneumonia, 1 each of carcinoma of the cervix (diagnosed after randomization), seizures, ischaemic heart disease. A further patient (THC group) died in week 42 from urinary and respiratory infections contracted during week 12 of the main study. Overall, there were no major safety concerns.

During the 15 weeks sub-study period [Freeman 2006] AEs involving the urinary tract were reported in 62 THC-treated and 73 placebo-treated patients. Most were urinary tract infections (35 and 42, respectively). Two episodes of urinary retention occurred in the THC group and 3 in the placebo group.

Cannabis extract vs. placebo

In the CAMS study reported above [Zajicek 2003, Zajicek 2005, Freeman 2006], urge incontinence episodes showed a 25% reduction in the cannabis group vs. placebo (p=0.005). Patients reporting

overall improvement in bladder function were 44% for cannabis vs. 33% for placebo. There were no significant differences in any of the King's Health Questionnaire domains.

During the 15 weeks sub-study period [Freeman 2006] AEs involving the urinary tract were reported in 64 cannabis-treated and 73 placebo-treated patients. Most were urinary tract infections (33 and 42, respectively). No episodes of urinary retention occurred in the cannabis group vs. 3 in the placebo group.

D9-Tetrahydrocannabinol (THC) vs. cannabis extract

In the CAMS study reported above [Zajicek 2003, Zajicek 2005, Freeman 2006], urge incontinence episodes showed a similar reduction (19% in the THC group vs. 25% in the cannabis group). Patients reporting overall improvement in bladder function were also similar (40% for THC and 44% for cannabis), and there were no significant differences in any of the King's Health Questionnaire domains. Occurrence of urinary tract infections did not differ between groups.

Nabiximols vs. placebo

Collin 2010 compared nabiximols (1:1 mix of THC and cannabidiol extracted from cloned cannabis sativa, available as an oromucosal spray; 2.7 mg THC and 2.5 mg CBD, up to 24 sprays/24 h) to placebo over 15 weeks in 337 MS patients. The primary endpoint was spasticity. Bladder symptoms were assessed using NRS. No differences between groups were found for bladder symptoms (NRS), ADL or quality of life (QOL) measures. A total of 55 patients (16%) discontinued treatment early: 35 (21%) in the nabiximols group and 20 (12%) in the placebo group. Of these 55 patients, 32 (58%) withdrew from the study. The primary reason given for withdrawal was AE occurrence: 9 patients (5%) on nabiximols and 5 (3%) on placebo. Two patients died from cancer during the study: neither death was considered to be related to the (active) study medication. The most common AEs were urinary tract infections, with no differences between groups.

Desmopressin vs. placebo

Valiquette 1996 conducted a crossover RCT comparing desmopressin, a synthetic analogue of vasopressin (10 µg intranasal spray at bedtime for 2 weeks), to placebo in 17 outpatients with severe MS and nocturia. Patients over 65 years and those with hypertension, thrombotic events, cardiovascular, thyroid, or renal disease were excluded. Patients recorded the number of nocturia episodes and incontinence episodes in a voiding diary.

The mean percentage of nights with episodes of nocturia was reduced from 97% to 66% on desmopressin vs. 97% to 95% on placebo ($p<0.01$). The mean number of episodes of nocturia per night was reduced from 2.3 to 1.1 on desmopressin vs. 2.3 to 2.1 on placebo ($p<0.01$). The maximum uninterrupted sleep hours increased from 3.7 to 5.8 on desmopressin vs. 3.7 to 4.3 on placebo ($p<0.01$). Eleven patients completed the 6-week trial. There were 5 drop outs: 4 for hyponatremia during desmopressin, one for lower urinary tract infection (unspecified treatment phase).

In conclusion, 6 trials assessed the efficacy of different drugs (antimuscarinics, cannabinoids, desmopressin). These drugs are generally used in combination with (self) catheterization in this population. A range of other drugs (e.g. new antimuscarinics, mirabegron) and neurostimulation/neuromodulation approaches are now available, which need to be proved effective in this population.

References

Collin C, Ehler E, Waberzinek G, et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurol Res 2010; 32: 451-459.

Fader M, Glickman S, Haggar V, Barton R, Brooks R, Malone-Lee J. Intravesical atropine compared to oral oxybutynin for neurogenic detrusor overactivity: a double-blind, randomized crossover trial. J Urol 2007; 177(1): 208-213.

Freeman RM, Adekanmi O, Waterfield MR, Waterfield AE, Wright D, Zajicek J. The effect of cannabis on urge incontinence in patients with multiple sclerosis: A multicentre, randomised placebo-controlled trial (CAMS-LUTS). Int Urogynecol J Pelvic Floor Dysfunct 2006; 17(6): 636-641.

Phé V, Chartier–Kastler E, Panicker JN. Management of neurogenic bladder in patients with multiple sclerosis. Nat Revi Urol 2016; 13: 276-288.

Valiquette G, Herbert J, Maede-D'Alisera P. Desmopressin in the management of nocturia in patients with multiple sclerosis. A double-blind, crossover trial. Arch Neurol 1996; 53(12): 1270-1275.

Zajicek J, Fox P, Sanders H, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet 2003; 362: 1517-1526.

Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry 2005; 76: 1664-1669.

4. Multidisciplinary rehabilitation (clinical question 6)

According to Wade (1992) rehabilitation is a problem-solving educational process aimed at reducing symptoms and limitations at the level of activity and participation. Multidisciplinary rehabilitation encompasses different interventions applied by a number of different (health) professionals as e.g. physiotherapists, physicians, nurses, occupational therapists, psychologists. It is frequently delivered in rehabilitation clinics on an in-patient or out-patient basis and sometimes at community centers or the patients' home. Khan 2007 defined multidisciplinary (also called interdisciplinary) rehabilitation as "an inpatient, outpatient, home or community-based coordinated intervention, delivered by two or more disciplines in conjunction with physician consultation (neurologist or rehabilitation medicine physician), which aims to limit patient symptoms, and enhance functional independence and maximize participation, as defined by ICF [International Classification of Functioning, Disability and Health]".

We found 11 publications reporting on 9 trials (8 RCTs and one controlled clinical trial) from 5 countries and different settings [Francabandera 1988, Di Fabio 1997, Di Fabio 1998, Freeman 1997, Gaugenti Tax 2000, Pozzilli 2002, Patti 2002, Patti 2003, Storr 2006, Papeix 2015, Pappalardo 2016]. The studies differed in terms of intervention components, duration and intensity of interventions, outcomes and length of follow-up. Therefore, we were unable to perform meta-analyses, and results were summarized descriptively. Overall we have low or very low certainty in our findings mostly due to risk of bias and imprecision. Publication bias cannot be ruled out.

Mostly participants receiving multidisciplinary rehabilitation had favorable outcomes compared to controls. All studies measured ADL and functioning using different scales and most measured QOL while other outcomes as participation or symptom burden were rarely assessed. Caregiver outcomes were only addressed in one study indicating no clear difference between multidisciplinary rehabilitation and standard care. Costs were assessed in one RCT indicating that home-based multidisciplinary rehabilitation was cost-effective. Adverse events were not reported.

In conclusion, multidisciplinary rehabilitation seems to have positive effects in patients with severe MS although the certainty of the evidence is low or very low.

References

Di Fabio RP, Choi T, Soderberg J, et al. Health-related quality of life for patients with progressive multiple sclerosis: influence of rehabilitation. Physical Therapy 1997; 77: 1704-1716.

Di Fabio RP, Soderberg J, Choi T, et al. Extended outpatient rehabilitation: its influence on symptom frequency, fatigue, and functional status for persons with progressive multiple sclerosis. Arch Phys Med Rehabil 1998; 79: 141-146.

Francabandera FL, Holland NJ, Wiesel-Levison P, Scheinberg LC. Multiple sclerosis rehabilitation: inpatient vs. outpatient. Rehabilitation nursing 1988; 13: 251-253.

Freeman JA, Langdon DW, Hobart JC, Thompson AJ The impact of inpatient rehabilitation on progressive multiple sclerosis. Ann Neurol 1997; 42: 236-244.

Gaugenti-Tax EM, DiLorenzo TA, Tenteromano L, et al. Impact of a comprehensive long-term care program on caregiver and person with multiple sclerosis. Int J MS Care 2000; 2: 5-18.

Khan F, Turner-Stokes L, Ng L, Kilpatrick T, Amatya B. Multidisciplinary rehabilitation for adults with multiple sclerosis. Cochrane Database Syst Rev 2007; 2: CD006036. DOI: 10.1002/14651858.CD006036.pub2.

Papeix C, Gambotti L, Assouad R, et al. Evaluation of an integrated multidisciplinary approach in multiple sclerosis care: A prospective, randomized, controlled study. Mult.Scler.J Exp Transl Clin 2015; 1: 2055217315608864.

Pappalardo A, D'Amico E, Leone C, et al. Inpatient versus outpatient rehabilitation for multiple sclerosis patients: Effects on disability and quality of life. Multiple Sclerosis and Demyelinating Disorders 2016; 1.

Patti F, Ciancio MR, Reggio E, et al. The impact of outpatient rehabilitation on quality of life in multiple sclerosis. J Neurol 2002; 249: 1027-1033.

Patti F, Ciancio MR, Cacopardo M, et al. Effects of a short outpatient rehabilitation treatment on disability of multiple sclerosis patients--a randomised controlled trial. J Neurol 2003; 250: 861-866.

Pozzilli C, Brunetti M, Amicosante AM, et al. Home based management in multiple sclerosis: results of a randomised controlled trial. J Neurol Neurosurg Psychiatry 2002; 73: 250-255.

Storr LK, Sorensen PS, Ravnborg M. The efficacy of multidisciplinary rehabilitation in stable multiple sclerosis patients. Multiple Sclerosis 2006; 12: 235-242.

Wade DT. *Measurement in neurological rehabilitation*. Oxford: Oxford University Press, 1992.

5. Interventions for caregivers (clinical questions 7 and 8)

Two clinical questions concerned interventions for caregivers, in terms of structured education and training programmes on caregiving, and of structured, practical and/or emotional support programmes (Appendix 2).

Out of 3572 records screened, 8 full text papers (seven studies) were assessed, and seven were excluded: three evaluated patient and caregiver needs [McKeown 2003, Buchanan 2009, Strupp 2017], two were on the development and pilot testing of an education program for caregivers of patients aging with MS [Finlayson 2008; Finlayson 2009], one on the development of a family adaptation model for spousal caregivers of patients with MS [Lee 2013], and one was a systematic review on interventions for families with patients having progressive neurological illnesses [Tams 2016].

The study included [Gaugenti-Tax 2000] was also included in clinical question 2 on multidisciplinary rehabilitation (see above). It was a RCT that compared a two-year, community-based, comprehensive care program for MS patients and caregivers units to usual care. The program addressed both clinical questions 6 and 7, as it included education as well as practical and emotional support for caregivers. Education for caregivers comprised 10 workshops that addressed coping with social, psychological, and medical aspects of MS and their impact on the caregiver. Practical support consisted of a one-year bimonthly patient day-care program that included group-based physical, occupational, and recreational therapy, group counseling with a social worker, socialization, nursing services, and lunch. Thirty units were assigned to the program and 29 to usual care. Health-related QOL of caregivers was assessed on a yearly basis for two years. A statistically significant change in favor of the program was found in three SF-36 subscales: general health, social functioning and physical role. Caregivers of the control group reported significant decreases in perceived health and health problems and caregiving activities interfered with social activities compared to caregivers of the intervention group. No obvious effect was found on patient outcomes. During the two years, 14/59 participants (24%) dropped out (figures by allocation group not provided). Four drop outs were due to patient death and one to caregiver death. Other drop out reasons were disease progression (n= 4), and transportation problems (n=5). Living too far away (n=28, 25%) and transportation problems (n=18, 16%) were the two main reasons for not participating in the RCT, pointing to a need for interventions that are not burdensome and fit with caregiving and family duties.

References

Buchanan RJ, Radin D, Chakravorty BJ, Tyry T. Informal care giving to more disabled people with multiple sclerosis. Disabil Rehabil 2009; 31(15): 1244–1256.

Finlayson M, Garcia JD, Preissner K. Development of an educational programme for caregivers of people aging with multiple sclerosis. Occup Ther Int 2008; 15: 4–17.

Finlayson M, Preissner K, Garcia J. Pilot study of an educational programme for caregivers of people ageing with multiple sclerosis. British Journal of Occupational Therapy 2009, 72(1), 11–19.

Gaugenti-Tax EM, DiLorenzo TA, Tenteromano L, et al. Impact of a comprehensive long-term care program on caregiver and person with multiple sclerosis. Int J MS Care 2000; 2: 5-18.

Lee EJ, DeDios S, Simonette C, Lee GK. Family adaptation model for spousal caregivers of people with multiple sclerosis: Testing the stress-processing theory. Journal of Vocational Rehabilitation 2013; 39(2): 91–100.

McKeown, LP, Porter-Armstrong AP, Baxter GD. The needs and experiences of caregivers of individuals with multiple sclerosis: A systematic review. Clin Rehabil 2003; 17(3): 234–248.

Strupp J, Groebe B, Knies A, Mai M, Voltz R, Golla H. Evaluation of a palliative and hospice care telephone hotline for patients severely affected by multiple sclerosis and their caregivers. Eur J Neurol 2017; 24(12): 1518–1524

Tams R, Prangnell SJ, Daisley A. Helping families thrive in the face of uncertainty: Strengths based approaches to working with families affected by progressive neurological illness. NeuroRehabilitation 2016; 38(3): 257–270.

6. Interventions for healthcare professionals (clinical questions 9 and 10)

Finally, two clinical questions concerned education and training for HPs: one concerned training in palliative care (PC) /specialist PC for MS HP, and one training in MS for PC HPs (Appendix 2).

Of 37 records screened, 2 were assessed as full text [Dallara 2014, Robinson 2014] and excluded from the final selection.

We found no evidence regarding the effectiveness of training in PC or specialist PC for HPs caring for patients with MS. We found no evidence regarding the effectiveness of training in MS for PC HPs. There is increasing discussion of the need for close collaboration between PC and neurology, and for neurologists to receive training in basic PC principles [American Academy 1996, Turner-Stokes 2008, Dallara 2014, Robinson 2014, Boersma 2014]. It has been recommended that neurologists should have familiarity and comfort with communicating bad news, engaging in end-of-life conversations and ACP, caregiver assessment, and other PC skills. On the other hand, PC teams may also need specialized training for managing MS patients. The required competencies can be achieved through enhanced joint training within the two specialties [Boersma 2014]. Despite efforts to improve the PC training of neurology resident physicians [Creutzfeld 2009], there is no evidence available as to its use or effectiveness and recommendations can only be made by consensus using the evidence from this literature [Oliver 2016].

References

American Academy of Neurology. Palliative care in neurology. The American Academy of Neurology Ethics and Humanities Subcommittee. Neurology 1996; 46: 870–872.

Boersma I, Miyasaki J, Kutner J, Kluger B. Palliative care and neurology: time for a paradigm shift. Neurology 2014; 83(6): 561-567.

Creutzfeldt CJ, Gooley T, Walker M. Are neurology residents prepared to deal with dying patients? Arch Neurol 2009; 66: 1427–1428.

Dallara A, Tolchin DW. Emerging subspecialties in neurology: Palliative care. Neurology 2014; 82(7): 640–642.

Oliver DJ, Borasio GD, Caraceni A, de Visser M, Grisold W, Lorenzl S, Veronese S, Voltz R. A consensus review on the development of palliative care for patients with chronic and progressive neurological disease. Eur J Neurol 2016; 23: 30-38.

Robinson MT, Barrett KM. Emerging subspecialties in neurology: Neuropalliative care. Neurology 2014; 82(21): e180–e182.