

Appendix 5: Summary table of all studies included in this review.

CANNABIS									
Study	Citations	Study type	Study population	Control type	Total study population analysed	Primary outcome measures	Class of evidence criteria	Class of evidence	Main result
Collin et al. 2007 [subset of CAMS study in Zajicek et al. 2003]	Collin et al. 2007	RCT (double-blind)	People with definite MS	Placebo	189	Respondent reported effect of cannabis; safety and/or tolerability; spasticity	Present: follow-up of ≥80%, random sequence generation, allocation concealment, blind assessment, intention-to-treat analysis; Absent: adequate sample size, equal intervention application (2:1 ratio)	II	Treatment resulted in a mean 21.5% decrease in Numeric Rating Scale score (spasticity), which was significantly greater than the control.
Freeman et al. 2006	Freeman et al. 2006	RCT (double-blind)	People with MS	Placebo	225	Incontinence	Present: adequate sample size, follow-up of ≥80%, random sequence generation, allocation concealment, blind assessment, equal intervention application, intention-to-treat analysis; Absent: none	I	Cannabis extract and THC reduced the adjusted incontinence episode rate by 38% and 33%, respectively, both significantly greater than the control (18% reduction).

Novotna et al. 2011	Novotna et al. 2011	RCT (double-blind)	People with MS whose spasticity was not fully relieved with current antispasticity therapy and who achieved 20% or greater improvement in 4 week single-blind Sativex (cannabis extract) treatment	Placebo	224	Spasticity	<p>Present: adequate sample size, follow-up of $\geq 80\%$, random sequence generation, allocation concealment, blind assessment, equal intervention application, intention-to-treat analysis;</p> <p>Absent: none</p>	I	Cannabis extract resulted in a mean 43.6% reduction (improvement) in Numeric Rating Scale score of spasticity, significantly greater than the control.
Rog et al. 2005	Rog et al. 2005	RCT (double-blind)	People with MS	Placebo	64	Pain; safety and/or tolerability	<p>Present: adequate sample size, follow-up of $\geq 80\%$, random sequence generation, allocation concealment, blind assessment, equal intervention application, intention-to-treat analysis;</p> <p>Absent: none</p>	I	Cannabis extract resulted in a mean 41.5% reduction in Numeric Rating Scale score of pain and a mean 48.9% reduction in pain-related sleep disturbance, significantly greater than control.

Wade et al. 2004	Wade et al. 2004	RCT (double-blind)	People with MS experiencing significant problems from at least one of the following: spasticity, spasms, bladder problems, tremor or pain	Placebo	154	Safety and/or tolerability; visual analogue score (VAS) of most troublesome symptom	Present: adequate sample size, follow-up of $\geq 80\%$, random sequence generation, allocation concealment, blind assessment, equal intervention application; Absent: intention-to-treat analysis	II	Cannabis extract reduced the Visual Analogue Score (VAS) among those with spasticity as their most troublesome symptom (significantly greater than the control), but no effect on the VAS generally.
Zajicek et al. 2003	Zajicek et al. 2003; Zajicek et al. 2005	RCT (double-blind)	People with MS	Placebo	611	Safety and/or tolerability; spasticity	Present: follow-up of $\geq 80\%$, random sequence generation, allocation concealment, blind assessment, equal intervention application; Absent: adequate sample size, intention-to-treat analysis	II	Cannabis extract and THC had no effect on Ashworth scale score (spasticity), but some effect on patient perception of symptom.
Zajicek et al. 2012	Zajicek et al. 2012	phase III clinical trial (double-blind)	People with MS	Placebo	279	Muscle stiffness	Present: follow-up of $\geq 80\%$, random sequence generation, allocation concealment, blind assessment, equal intervention application; Absent: adequate sample size, intention-to-treat analysis	II	Cannabis had positive effect on the patient-reported category rating scale score for muscle stiffness, significantly greater than for the control.

DIET

Study	Citations	Study type	Study population	Control type	Total study population analysed	Primary outcome measures	Class of evidence criteria	Class of evidence	Main result
Lovera et al. 2012	Lovera et al. 2012	RCT (double-blind)	People with MS	Placebo	116	MRI and/or cognitive function metrics; safety and/or tolerability	Present: adequate sample size, follow-up of $\geq 80\%$, random sequence generation, allocation concealment, blind assessment, equal intervention application, intention-to-treat analysis; Absent: none	I	<i>Ginkgo biloba</i> had no effect on cognitive performance.
Mosayebi et al. 2011	Mosayebi et al. 2011	RCT (double-blind)	People with MS	Placebo	59	Immune markers; MRI and/or cognitive function metrics; relapse and/or disability	Present: follow-up of $\geq 80\%$, random sequence generation, allocation concealment, blind assessment, equal intervention application; Absent: adequate sample size, intention-to-treat analysis	II	Vitamin D supplementation had no effect on gadolinium-enhancing MRI lesions or disability. However, at the 6 month follow-up, treated patients had significantly lower cell proliferation and higher levels of transforming growth factor (79.3%) and interleukin-10 (37.5%), significantly better than the control group.

Rezapour-Firouzi et al. 2013a	Rezapour-Firouzi et al. 2013a; Rezapour-Firouzi et al. 2013b; Rezapour-Firouzi et al. 2014; Rezapour-Firouzi et al. 2015	RCT (double-blind)	People with RRMS patients with EDSS<6	Placebo (olive oil)	65	Immune markers; relapse and/or disability	Present: random sequence generation, allocation concealment, blind assessment, equal intervention application; Absent: adequate sample size, follow-up of ≥80%, intention-to-treat analysis	II	PUFA-rich oil supplementation, with and without a Hot-natured diet, significantly reduced EDSS by a mean of 35.9% and 43.7% and reduced relapse rate by a mean of 87.1% and 88.4%, respectively, over 6 months. However, while EDSS increased by a mean of 11.9% in the control group, there are no statistical comparisons between control and treatment groups.
Soilu-Hänninen et al. 2012	Soilu-Hänninen et al. 2012	RCT (double-blind)	66 MS patients; 32 in vitamin D intervention group	Placebo	62	MRI and/or cognitive function metrics; relapse and/or disability; safety and/or tolerability	Present: follow-up of ≥80%, random sequence generation, allocation concealment, blind assessment, equal intervention application; Absent: adequate sample size, intention-to-treat analysis	II	Vitamin D3 supplementation as an add-on treatment to interferon beta reduced the number of T1 gadolinium-enhancing MRI lesions by 83.3%, a significantly greater reduction than the control, but had no effect on burden of disease or disability accumulation.

Steffensen et al. 2011	Steffensen et al. 2011; Kampman et al. 2012; Rosjo et al. 2015	phase II trial (double-blind RCT)	Fully ambulatory people with MS patients	Placebo (calcium tablet)	68	Bone mineral density; fatigue, depression and/or QoL; inflammation markers; relapse and/or disability	Present: follow-up of ≥80%, random sequence generation, allocation concealment, blind assessment, equal intervention application, intention-to-treat analysis; Absent: adequate sample size	II	Vitamin D3 supplementation did not prevent bone loss or effect clinical outcomes, including inflammation markers, fatigue and depression.
Torkildsen et al. 2012	Torkildsen et al. 2012	RCT (double-blind)	People with MS	Placebo	92	MRI and/or cognitive function metrics	Present: adequate sample size, follow-up of ≥80%, random sequence generation, allocation concealment, blind assessment, equal intervention application; Absent: intention-to-treat analysis	II	No effect of omega-3 supplementation on gadolinium-enhancing MRI lesions or secondary outcomes.
Tourbah et al. 2016	Tourbah et al. 2016	RCT (double-blind)	People with progressive MS	51 completed RCT, 42 completed long-term follow-up where they were treated with biotin	154	Relapse and/or disability	Present: adequate sample size, follow-up of ≥80%, random sequence generation, allocation concealment, blind assessment, intention-to-treat analysis; Absent: equal intervention application	II	High dose biotin resulted in disability reversal at month 9, confirmed at month 12, in 12.6% of treated patients, significantly more than the control (0 patients).

EXERCISE

Study	Citations	Study type	Study population	Control type	Total study population analysed	Primary outcome measures	Class of evidence criteria	Class of evidence	Main result
Bansi et al. 2012	Bansi et al. 2012; Bansi et al. 2013	RCT (single-blind)	People with MS	Compared aquatic and land-based exercises	52	Endurance improvement; fatigue, depression and/or QoL; immune markers	Present: follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application; Absent: adequate sample size, allocation concealment, intention-to-treat analysis	II	No significant differences in cytokines and neurotrophins between exercise treatments. Cardiovascular metrics improved in both groups, but there was no significant difference between the two.
Collett et al. 2010	Collett et al. 2010	RCT (single-blind)	People with MS	Compared continuous, intermittent, and combined exercise regimes	55	Gait speed	Present: adequate sample size, follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application, intention-to-treat analysis; Absent: allocation concealment	II	Exercise improved walking speed (effect size = 0.25), but its effect did not vary between intensity treatments.

Dodd et al. 2011	Dodd et al. 2011	RCT (single-blind)	People with RRMS	Usual care	67	Endurance improvement; gait speed	Present: follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application, intention-to-treat analysis; Absent: adequate sample size, allocation concealment	II	No effect of progressive resistance training (PRT) on the primary outcome of walking performance. However, PRT improved several secondary outcomes, but this effect was not maintained at the 22-week follow-up.
Gandolfi et al. 2015	Gandolfi et al. 2015	RCT (single-blind)	People with MS (EDSS: 1.5– 6.0) and subjective symptoms of balance disorders	Conventional rehabilitation	80	Balance	Present: follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application, intention-to-treat analysis; Absent: adequate sample size, allocation concealment	II	Sensory integration balance training improved balance by 10% (Berg Balance Scale), significantly more than the control. Also reduced secondary outcome of fatigue by 14.6% (FSS).
Garrett et al. 2012	Garrett et al. 2012	RCT (single-blind)	People with MS	No intervention	291	Functional impairment; MRI and/or cognitive function metrics	Present: follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application; Absent: adequate sample size, allocation concealment, intention-to-treat analysis	II	Group physical therapist-led and fitness-instructor led exercise programs improved the MS Impact Scale physical component significantly compared to the control. Yoga did not. All interventions improved the secondary outcomes,

except that yoga did not improve the 6 MWT.

Nilsagard et al. 2012	Nilsagard et al. 2012	RCT (single-blind)	People with MS	No intervention	80	Timed Up and Go test (TUG)	Present: follow-up of $\geq 80\%$, random sequence generation, blind assessment, equal intervention application; Absent: adequate sample size, allocation concealment, intention-to-treat analysis	II	Nintendo Wii Fit® balance training had no effect on walking ability or balance.
Oken et al. 2004	Oken et al. 2004	RCT (single-blind)	People with MS	Waitlist	57	MRI and/or cognitive function metrics	Present: follow-up of $\geq 80\%$, random sequence generation, blind assessment, equal intervention application, intention-to-treat analysis; Absent: adequate sample size, allocation concealment	II	Neither aerobic exercise nor yoga had an effect on alertness or attention.

Romberg et al. 2004	Romberg et al. 2004; Romberg et al. 2005	RCT (not blinded)	People with MS with mild to moderate disability	No intervention	91	Fatigue, depression and/or QoL; functional impairment; gait speed; relapse and/or disability	Present: follow-up of ≥80%, random sequence generation, equal intervention application, intention-to-treat analysis; Absent: adequate sample size, allocation concealment, blind assessment	II	A 6-month exercise program improved walking speed by 11.6%, significantly more than the control. However, it had no effect on HR-QoL.
Straudi et al. 2016	Straudi et al. 2016	RCT (single-blind)	People with MS (EDSS 6.0–7.0)	Conventional walking therapy	52	Endurance improvement; gait speed	Present: adequate sample size, follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application, intention-to-treat analysis; Absent: allocation concealment	II	Robot-assisted gait training significantly improved walking endurance and balance compared to control. Effect size could not be determined.
Tarakci et al. 2013	Tarakci et al. 2013	RCT (single-blind)	Ambulatory people with MS	No intervention	99	Balance; gait speed	Present: adequate sample size, follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application, intention-to-treat analysis; Absent: allocation concealment	II	Supervised group exercise training improved balance by 11.5% (Berg Balance Score) and walking speed by 15.2% and 20.6% (10 MWT and 10 SCT). It also improves the secondary outcome of fatigue by 21% (FSS).

PSYCHOLOGICAL APPROACHES

Study	Citations	Study type	Study population	Control type	Total study population analysed	Primary outcome measures	Class of evidence criteria	Class of evidence	Main result
Grossman et al. 2010	Grossman et al. 2010	RCT (not blind)	People with MS	Usual care	150	Fatigue, depression and/or QoL	<p>Present: adequate sample size, follow-up of ≥80%, random sequence generation, equal intervention application, intention-to-treat analysis;</p> <p>Absent: allocation concealment, blind assessment</p>	II	Mindfulness treatment improved disease aspecific HR-QoL (PQOLC, effect size =0.51), disease specific HR-QoL (HAQUAMS, effect size = 0.28), depression (CES-D, effect size = 0.36), and fatigue (MFIS, effect size = 0.38). All improvements were significantly greater than the control.
Lincoln et al. 2011	Lincoln et al. 2011	RCT (single-blind)	People with MS patients with low mood	Waitlist	127	Anxiety, distress and/or stress; fatigue, depression and/or QoL; MS Impact Scale (MSIS)- Psychological	<p>Present: follow-up of ≥80%, random sequence generation, equal intervention application, intention-to-treat analysis;</p> <p>Absent: adequate sample size, allocation concealment</p>	II	CBT improved general health score (General Health Questionnaire 12) by 5.5% , reduced depression by 5.8% (Beck Depression Inventory) and 7.9% (HADS), and reduced anxiety by a mean of 9.8% (HADS). These effects were significant compared to the control.

Mohr et al. 2001	Mohr et al. 2001; Mohr et al. 2003; Mohr et al. 2004	RCT (not blind)	People with MS	sertraline (antidepressant) and supportive-expressive therapy (SEG)	52	Fatigue, depression and/or QoL; social support	Present: follow-up of ≥80%, random sequence generation, equal intervention application, intention-to-treat analysis; Absent: adequate sample size, allocation concealment	II	CBT and sertraline were more effective than SEG at reducing depression. Treatments for depression lead to reductions in fatigue (CBT reduced Fatigue Assessment Instrument score by 6.5%), likely due to change in mood, and treatment for depression increased sense of support.
Mohr et al. 2005	Mohr et al. 2005; Hart et al. 2008; Beckner et al. 2010; Cosio et al. 2011; Baron et al. 2011	RCT (single-blind)	People with MS	Supportive emotion focused therapy	127	Affect, benefit-finding and/or optimism; fatigue, depression and/or QoL; insomnia; relapse and/or disability; social support	Present: follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application; Absent: adequate sample size, allocation concealment, intention-to-treat analysis	II	CBT improved QoL compared to control. Both treatments reduced insomnia by improving depression, but there was no statistical difference between the two. Effect sizes could not be calculated.
Mohr et al. 2007	Mohr et al. 2007; Blackmore et al. 2011	RCT (single-blind)	People with MS with depression	Supportive emotion focused therapy	127	Anxiety, distress and/or stress; functional impairment	Present: follow-up of ≥80%, random sequence generation, blind assessment,	II	Both treatments significantly improved disability and fatigue, but CBT was significantly more effective. Effect sizes

Moss-Morris et al. 2013	Moss-Morris et al. 2013	RCT (single-blind)	Ambulatory people with MS within 10 years of diagnosis	Supportive listening	94	Fatigue, depression and/or QoL; relapse and/or disability	<p>equal intervention application, intention-to-treat analysis;</p> <p>Absent: adequate sample size, allocation concealment</p> <p>Present: adequate sample size, follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application, intention-to-treat analysis;</p> <p>Absent: allocation concealment</p> <p>Present: follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application, intention-to-treat analysis;</p> <p>Absent:</p>	II	<p>could not be calculated.</p> <p>CBT reduced distress by 19.2% 12 months after treatment (GHQ-12), but had no effect on functional impairment (WSAS).</p> <p>Both treatment and control improved cognitive function as measured by the Minimal Assessment of Cognitive Function in MS. The treatment did show significantly greater improvement in the use of compensatory strategies.</p>
Stuifbergen et al. 2012	Stuifbergen et al. 2012	RCT (single-blind)	People with MS	Waitlist	61	MRI and/or cognitive function metrics	<p>equal intervention application, intention-to-treat analysis;</p> <p>Absent: adequate sample size, allocation concealment</p> <p>Present: adequate sample size, follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application, intention-to-treat analysis;</p> <p>Absent: allocation concealment</p> <p>Present: follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application, intention-to-treat analysis;</p> <p>Absent:</p>	II	<p>could not be calculated.</p> <p>CBT reduced distress by 19.2% 12 months after treatment (GHQ-12), but had no effect on functional impairment (WSAS).</p> <p>Both treatment and control improved cognitive function as measured by the Minimal Assessment of Cognitive Function in MS. The treatment did show significantly greater improvement in the use of compensatory strategies.</p>

							adequate sample size, allocation concealment		
Thomas et al. 2013	Thomas et al. 2013; Thomas et al. 2014; Thomas et al. 2015	RCT (single-blind)	People with MS	Current local practice	146	Fatigue, depression and/or QoL	<p>Present: follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application;</p> <p>Absent: adequate sample size, allocation concealment, intention-to-treat analysis</p>	II	CBT-based fatigue management program reduced fatigue severity and self-efficacy at 4 months follow-up (standardized effect sizes (SES) of -0.35 and 0.36, respectively) and 1 year follow-up (SES of -0.29 and 0.34, respectively). Significantly more effective than the control.
van Kessel 2008	van Kessel 2008; Knoop et al. 2012	RCT (not blind)	People with MS	Relaxation training	70	Affect, benefit-finding and/or optimism; fatigue, depression and/or QoL	<p>Present: adequate sample size, follow-up of ≥80%, random sequence generation, equal intervention application, intention-to-treat analysis;</p> <p>Absent: allocation</p>	II	Both are clinically effective treatments for fatigue in MS patients, although the effects for CBT are greater than those for the control (effect size of 3.03 for the treatment group and 1.83 for the control group).

concealment,
blind assessment



OTHER CAM

Study	Citations	Study type	Study population	Control type	Total study population analysed	Primary outcome measures	Class of evidence criteria	Class of evidence	Main result
Artemios et al. 2012	Artemiadis et al. 2012	RCT (single-blind)	People with RRMS	No intervention	61	Anxiety, distress and/or stress; fatigue, depression and/or QoL	Present: adequate sample size, follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application; Absent: allocation concealment, intention-to-treat analysis	II	Relaxation-based stress management program significantly reduced stress (Perceived Stress Scale, effect size = 0.62) and depression (Beck Depression Inventory, effect size = 0.53) compared to the control.
Bastani et al. 2015	Bastani et al. 2015	RCT (not blind)	Women with MS	Sham (touching, but no pressure)	100	Fatigue, depression and/or QoL	Present: adequate sample size, follow-up of ≥80%, random sequence generation, allocation concealment, equal intervention application; Absent: allocation concealment, blind assessment, intention-to-treat analysis	II	Acupressure reduced fatigue score by 26% (measured with the Fatigue Severity Scale).
Hughes et al. 2009	Hughes et al. 2009	RCT (single-blind)	People with MS	Sham reflexology	73	Pain	Present: adequate sample size, follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application; Absent: allocation	II	Both treatment and sham caused a significant reduction in pain that persisted to the 12-week follow-up. No significant difference between

							concealment, intention-to-treat analysis	treatment and sham effect.
Morrow et al. 2015	Morrow et al. 2015	RCT (double-blind)	People with MS demonstrating PS impairment on either the Symbol Digit Modalities Test (SDMT) or Paced Auditory Serial Addition Test (PASAT) XR(n=20)	Placebo	52	MRI and/or cognitive function metrics	Present: follow-up of ≥80%, random sequence generation, allocation concealment, blind assessment, equal intervention application; Absent: adequate sample size, intention-to-treat analysis	II Improving processing speed
Nazari et al. 2016	Nazari et al. 2016	RCT (single-blind)	Women with MS	Usual care, and relaxation	75	Pain	Present: follow-up of ≥80%, random sequence generation, blind assessment, equal intervention application; Absent: adequate, sample size, allocation concealment, intention-to-treat analysis	II Both relaxation and reflexology improve pain immediately after treatment (reduce Numerical Rating Scale score by 11.8% and 44.8%, respectively), but reflexology causes a greater reduction in pain than relaxation. However, neither caused a long-term effect (there was no difference between treatment and control at the 2-month follow-up).

