Database of Knowledge Translation Tools
Intervention Summary

1. Cognitive Behavioral Treatment for Fatigue in Multiple Sclerosis

Summary Author: Marit Ewen, OT
Date Published: *PENDING*

2. Intervention Description and Dose Recommendations

Purpose of the intervention:

Cognitive Behavioral Therapy (CBT) aims to improve MS-related fatigue by influencing thoughts, emotion, external factors and behaviors that may be contributing to fatigue related experiences.

- Individually-tailored, cognitive-behavioral approaches are preferred (Wendebourg, Heesen, Finlayson, Meyer, Pôttgen & Kôke, 2017)
- Model integrates biological and psychosocial research (van Kessel, Moss-Morris, Willoughby, Chalder, Johnson & Robinson, 2008)
- Topics covered include how to: (van den Akker, Beckerman, Collette, Eijssen, Dekker, de Groot 2016).
  - identify and deal with unhelpful thoughts
  - perform activity scheduling
  - identify and deal with stressors
  - continue to employ learned skills and how to deal with possible relapses

Recommended dose (Asano et al. 2015): More research is necessary to *strongly recommend* CBT, however, use of the program in conjunction with clinical decision-making is warranted

- Frequency: 1 session per week for 8-10 weeks, consider booster sessions after 8-10 weeks
- Intensity: Not applicable
- Time: No less than 50 minutes
- Type: Individual sessions include at least 3 face-to-face sessions. It is possible to choose for example 5 telephone sessions, to reduce potential stress of travel for the participants.
- Topics covered: Introduction to CBT and fatigue; Activity scheduling; Changing unhelpful thinking about fatigue; Sleep hygiene; Managing negative emotions; Role of social support (details available here)
  - Provided a manual with chapters of information for each week and homework sheets.
  - Format each session: Questions from previous week. Review homework. Introduction of new topic. Setting new practice tasks. Summary and questions.

In addition, goal-setting is recommended to focus attention on the goal (Akbar, Turpin, Petrin, Smyth Finlayson 2018) (Norsk MS veileder 2016).

3. Considerations for Clinical Use

Knowledge Expert group recommendation for application: *Pending*

Considerations:

- CBT demonstrated positive short-term effects, but effects may diminish with time
- Treatment recommendations are based on:
  - 4 studies on the impact of CBT programmes, 3 demonstrated a positive outcome
  - 2 studies assessed delivering the program online, but the treatment was less effective.
  - In the studies with better outcomes, the CBT-intervention was provided by psychologists with CBT training (CBT Interventionists)

- No access (in Norwegian) to CBT manuals or protocols from these studies:
  - van Kessel protocol in English, not Norwegian
  - TREFAMS-CBT protocol exists in Dutch, not English or Norwegian

  Norwegian health professionals and patients could consider the self-help program for fatigue at http://www.kognitiv.no:
  - Available online, 9 hours of self-help education, themes include: biopsychosocial understanding of fatigue, daily activity and activity scheduling, cognitive strategies and how to implement this in the future.
- Other treatment options are available and may include aerobic training and/or other fatigue management programs

4. Appropriate Patients for the Intervention

Diagnosis: Multiple Sclerosis, patients studied were Relapsing-Remitting (40-60% of the participants), secondary progressive (20-30%) and primary progressive (3% to 10%)

Sample descriptions: Heterogeneous samples with a variety of age, disability and type of MS. Participants were predominantly women, ~41-56 years. All types of MS, predominantly Relapsing Remitting MS, diagnosed since 5.5-21 years. Samples included patients who are able to walk with or without an aid for at least 100 meters.

Current level of function: Studies generally included patients:
- EDSS≤ 6 (able to ambulate ≥ 100 meters with/without aid)
- Fatigue Severity Scale or Fatigue Scale score > 4 (fatigue that impacts daily life)

5. Recommended Outcome Measures

CBT may improve:(Wendebourg et al 2017)
- Fatigue severity (intensity and characteristics of the experienced fatigue)
  - Fatigue Severity Scale (see measure description online; available in Norwegian)
- Fatigue impact (the activities difficult to do because of fatigue)
  - Fatigue Impact Scale (see measure description online)
  - Modified Fatigue Impact Scale (see measure description online)
  - Chalder Fatigue Scale (see test; available in Norwegian)
  - Fatigue scale for motor and cognitive functions (see test)
  - Patient Reported Outcomes Measurement Information System (PROMIS)-fatigue (see measure description online; available in Norwegian)
  - FSMC-Norwegian are recommended for mental fatigue assessment (Norsk Veileder 2016)

Screening for depression, anxiety, and cognition – consider referring to psychologist or neuropsychologist if positive
- Depression and anxiety, measures used in research included:
  - Hospital Anxiety and Depression Scale (see measurement description online)
  - Beck Depression Inventory (see measurement description online)
- Cognitive measure, some examples below:
  - Repeatable Battery for the assessment of Neuropsychological Status
  - Brief International Assessment of Cognition for MS
  - MS Neuropsychological Questionnaire (available in Norwegian)

  If screening test is positive, consider referring to a neuropsychologist to determine if treatment is warranted.

Measurement timing:

- Fatigue assessment should be collected minimum 3 times, during the first session, halfway through, and within 1-2 sessions of discharge.
- Depression, anxiety, cognition assessments should be conducted during the first session

Other considerations: Doctors may want to assess for low hemoglobin, hypothyroidism, or other medical disorders that may cause fatigue

6. Overview of the Literature

Brief overview of theoretical basis for intervention:

Fatigue definition:

- No accepted definition of fatigue, studies do not define fatigue, differentiate between fatigue types, depression, or cognitive dysfunctions. (Brenner&Piehl 2016).
- In general, it is the abnormal feeling of tiredness and/or increased weakness after exercise or over the course of the day (Miller & Soundy 2017)
- The interventions aim to improve *fatigue severity* and/or *fatigue impact*.
  - *Fatigue severity:* intensity and the characteristics of the experienced fatigue
  - *Fatigue impact:* activities the patient cannot do because of fatigue (Wendebourg, Heesen, Finlayson, Meyer, Pôttgen & Kôke 2017).

Primary and secondary mechanisms of fatigue

- Multidimensional cause and consequences, includes psychological and biological factors (van Kessel, Moss-Morris 2006).
- Primary mechanism: disease process of the central nervous system
- Secondary mechanism: weakness, stiffness, tremor, disturbed sleep or negative emotions.
- Unknown cause, diverse consequences, and lack of precise measurement of the impact of fatigue, lead to a challenge to develop and prescribe effective intervention (Asano & Finlayson 2014)

Role of thoughts and beliefs

- A perception of the illness as uncontrollable or unpredictable might be associated with fatigue (Brenner & Piehl 2016)
- Depression, cognition and fatigue seem to be interrelated in a complex way in MS patients. (Brenner & Piehl 2016).
  - Fatigue is harder to treat when an untreated depression is present. Depression also affects information processing, working memory and executive functions.
  - Cognitive dysfunction influences 40% of MS patients, and mostly affects information processing speed, learning, memory and executive functions. Fatigue is associated with decreased attention and vigilance. The lack of a clear a definition and distinction between fatigue and cognition leads to therapeutic challenges.
- Two behavioral patterns are associated with fatigue (van Kessel, Moss-Morris 2006)
  - Avoiding activity or constantly resting can lead to deconditioning and may intensify fatigue
  - “Push and crash:” over-doing activities and then requiring rest for prolonged times

The cognitive behavioural model of MS fatigue proposes that biology, cognition, emotion and behavior influence one another (van Kessel, Moss-Morris 2006) and may improve fatigue

- Avoiding physical activity: advise a graded exercise program, provide information and strategies to change beliefs related to doing less
- Push and crash pattern: advise a consistent pattern of paced activity and rest
- Little control over symptoms: explore aspects of their life where they have some control and learn strategies to increase control.

- In research, CBT resulted in:(van den Akker et al 2018)
  - Improved fatigue perceptions
  - Increased physical activity
  - Decreased sleepiness
  - Post-treatment increases in fatigue levels were mediated by reduced physical activity, reduced concentration, and increased sleepiness

Meta-analyses on the effects of CBT

Fatigue severity:

Wendebourg, et al. 2017

- *Minimal to small effect size* favoring CBT in 4 studies (Mohr 2003; Moss-Morris, 2012; Thomas, 2013; van Kessel, 2010; Standard Mean Difference -0.60, Confidence Interval: -1.08, -0.11)
  - Compared to non-CBT approaches in 2 studies (Finlayson 2011 and Hugos 2009) that demonstrated almost no effect (Standard Mean Difference -.20, Confidence interval: -.60, .19)

van den Akker et al, 2016: Summary of CBT results: Small to Medium short-term effect, small long-term effects. CBT should be considered an evidence-based therapy for MS-related fatigue.

- *Small to medium effect size* favoring CBT in 4 studies that demonstrated a positive short-term outcome in reducing fatigue severity after 8-10 weeks. (Standard Mean Difference -0.47, 95% Confidence Interval: -.88, -0. 06)
- *Small effect size* favoring CBT in 3 long-term follow-up (Standard Mean Difference -30, 95% Confidence Interval: -0.51, -0.08)

Asano and Finlayson, 2014:

- *Large effect size* favoring CBT interventions (better outcomes compared to energy conservation and mindfulness)
  - CBT studies summarized:
    - Moss-Morris et al 2012: *Large effect size:* 1.11, 95%CI: 0.43-1.78
    - van Kessel et al 2008: *Large effect size:* 0.99, 95%CI: 0.50-1.48
    - Mohr et al 2003: *Large effect size:* 0.80, 95%CI: 0.19-1.42.
  - Energy conservation studies summarized:
    - Finlayson et al 2011: *Medium effect size:* 0.53, 95%CI:0.19-0.86
    - Mathiowetz et al 2005: *Small to Medium effect size:* 0.42, 95%CI: 0.08-0.76
  - Mindfulness study summaries:
    - Grossman et al 2010: *Small to Medium effect size:* 0.42, 95% CI: 0.09-0.74

Miller and Soundry, 2017: CBT and other behavioral interventions were identified as resulting in improvement on MS fatigue in 5 reviews. Recommended generic psycho-behavioral interventions with moderate confidence for the treatment of fatigue.

Asano, Berg, Johnson, Turpin& Finlayson 2015:

- van Kessel et al 2008: Effect size: *Large effect size* 2.99 compared to Relaxation therapy with smaller, but still large, effect size 1.79.
- Mohr et al 2003: *Moderate effect size* of CBT intervention 0.52, compared to group psychotherapy with *small and negative effect size* -0.15
- Thomas et al 2010 : *small and negative effect size* 0.12

Fatigue impact: not sufficient data to analyze to determine the effect (Wendebourg, et al. 2017)

Practice guidelines that include CBT:

NICE guideline (NICE 2014):

- Recommends health professionals to consider fatigue management program, advise patients that programs of aerobic and balance and stretching exercises including yoga may also be helpful in treating MS-related fatigue.
- Supervised exercise programs involving moderate progressive resistance training can be considered. If more than one of the interventions recommended for mobility or fatigue are suitable, offer treatment based on which the person prefers

Single Randomized controlled studies that include CBT: (Beckerman, Blikman, Heine, Malekzadeh, Teunssen, Bussmann, Kwakkel, van Meeteren, de Groot 2013; van den Akker, 2017)

Van den Akker et al. 2017:

- Significant effect of CBT on severe MS fatigue after treatment, the positive effect gradually lessened (absolute risk reduction of clinically relevant change was 0.31, the 95% Confidence Interval is 0.09-0.52; Number Needed to Treat = 3.3)

Thomas et al 2013: CBT and energy effectiveness training based on the Packer manual. Fatigue Applying Cognitive behavioural and Energy effectiveness Techniques to lifestyle (FACETS).
6 weekly sessions, 90 mins duration, group intervention.

Outcomes: Mean improvement in Fatigue Assessment Instrument was 0.1 (-0.2-0.4; within the SEM of the measurement).
NNT=5

	FACETS **Mean (SD), *p value for comparison with CLP***	**CLP (control)** **Mean (SD)**
Global Fatigue Severity Scale : Subscale of the Fatigue Assessment Instrument(FAI) *Most clinically relevant - Authors provided MCID of 0.5*	**Baseline:** 5.60(0.98) **F/U 1**: 5.48(0.92), *p value: .86* **F/U 2**: 5.26(1.03), *p value: .01* *Although statistically significant, doesn't exceed MCID indicating the change is not clinically significant.*	**Baseline**:5.61(1.09) **F/U 1:** 5.55(1.17) **F/U 2:** 5.66 (0.93)
MSIS-29	**Baseline:** 49.6(19.1) **F/U 1:** 47.3(18.2). p=0.46, *p value: .46* **F/U 2:** 44.9(19.2).p=0.53, *p value: .53*	**Baseline:** 43.9(17.6) **F/U 1:** 42.2(18.4) **F/U 2:** 43.0(17.3)
Fatigue Self-Efficacy Scale	**Baseline:** 45(17) **F/U 1:** 57(17), *p value: .001* **F/U 2:** 56(19), *p value: .0048*	**Baseline:** 49(16) **F/U 1:** 50(17) **F/U 2:** 53(17)

Effects of CBT online programs:

- Wendebourg et al, 2017: Web based interventions tailored to suit individual characteristics tend to be more effective than generic programs
- Van Kessel et al, 2016: Email support during online intervention positively influenced adherence. Treatment adherence was low.
- Moss Morris et al, 2012: Adherence to internet self-management program MSInvigour8 was low.
- Akbar et al, 2018: 66% completed MS INFoRm, a self-directed interactive Microsoft PowerPoint presentation.
- Asano, Berg, Johnson, Turpin& Finlayson 2015: Moss-Morris et al 2012: CBT online had effect size 1.03 compared to usual care which had effect size -0.04.

Group vs individual treatment:

- Wendebourg et al, 2017: Individual treatment is slightly more effective than group approaches in reducing fatigue severity
  - *Large Effect* with Individual approaches: Standardized response mean -0.80, 95%Confidence Interval: -1.13 to -0.47
  - *Minimal to small effe*ct with group approaches: Standardized response mean -0.17, 95%Confidense Interval: -0.39 to 0.05

7. Documentation Tips:

Components to include in documentation: *Pending*

8. Links to other relevant resources:

Websites:

- Norsk Forening for Kognitiv Terapi: NFKT, http://www.kognitiv.no
- Applying Evidence with Confidence Website, https://www.appeco.net/

9. References:

Sample information:

Mohr et al. 2003: RCT, comparing CBT, psychotherapy and sertraline for improvements in fatigue and mood to 16 week treatments. Sample size N= 60. Average age 44.6. 71.7% women. The mean AI was 2,45, meaning patients ranged from no symptoms to requiring a wheelchair for mobility, but on average showed mild to moderate gait impairments.

Moss-Morris et al 2012: Sample size N=40. CBT-intervention. Mean age 40.14, 69% women. Able to walk 500 m or longer 39.1%, able to walk with an aid 39.1%. MS type: 43.5% RR, 30.4% SP, 8.7% PP.

Thomas et al 2013: RCT. Sample size N= 164. 73% women. Mean age 48. Type of MS: 43% RR, 20%SP, 6%PP. APDSS score 22% no limitations on walking. 46% MS interferes with walking, 32% needs walking aid. Compared FACETS to current local practice. CBT and energy effectiveness training based on the Packer manual. Fatigue Applying Cognitive behavioural and Energy effectiveness Techniques to lifestyle (FACETS).

Van Kessel et al 2008: RCT. Sample size N= 72. CBT program, compared to relaxation training. Mean age 42.89, 80% female. Mean EDSS 3.04. Type of MS: 65.7% RR, 31.4% SP, 2.9%PP.

Van den Akker et al(2017): RCT. Compared 12 individual sessions with CBT to 3 consultations with a MS nurse, both programs delivered over 16 weeks. Assessment at baseline, 8 weeks, 16 weeks(post-intervention), 26 and 52 weeks post-baseline. N=91. Mean age: 50.6. 70.5% women. EDSS score 3.0. Type of MS: 72.7% Relapsing Remitting(RR), 13.6% Primary Progressive(PP) and 11.4% Secondary Progressive(SP). HADS depression: 5.6, HADS anxiety 6.7.

1. Akbar N, Turpin K, Petrin J, Smyth P & Finlayson M. A pilot mixed-methods evaluation of MS INFoRm: a self-directed fatigue management resource for individuals with multiple sclerosis. International Journal of Rehabilitation Research. Vol00 No00. 2018
2. Asano M, Berg E, Johnson K, Turpin M & Finlayson M. A scoping review of rehabilitation interventions that reduce fatigue among adults with multiple sclerosis.(2015) Disability and Rehabilitation, 37:9, 729-738.
3. Asano M, Finlayson ML. Meta-Analysis of Three Different Types of Fatigue Management Interventions for People with Multiple Sclerosis: Exercise, Education and Medication. Mult Scler Int 2014;2014
4. Beckerman H, Blikman LJM, Heine M, Malekzadeh, Teunssen CE, Bussmann JBJ, Kwakkel G, van Meeteren J, de Groot V, the TREFAMS-ACE study group. The effectiveness of aerobic training, cognitive behavioral therapy, and energy conservation management in treating MS-related fatigue: the design of the TREFAMS-ACE programme. Trials 2013; 14: 250. Published online 2013 Aug 12. doi: 10.1186/1745-6215-14-250
5. Blikman LJ, Huisstede BM, Kooijmans H, Stam HJ, Bussmann JB, van Meeteren J. Effectiveness of energy Conservation Treatment in reducing fatigue in Multiple Sclerosis: A systematic review and meta-Analysis. Archives of Physical medicine and Rehabilitation 2013;94:1360-76.
6. Brenner P & Piehl F. Fatigue and depression in multiple sclerosis: pharmacological and non-pharmacological interventions. Acta Neurologica Scandinavica 2016;134(Suppl.200):47-54.

7. Finlayson M, Preissner K, Cho C, Plow M. Randomized trial of a teleconference-delivered fatigue management program for people with multiple sclerosis. Multiple Sclerosis. 2011;17(9):1130–1140.
8. Grossman P, Kappos L, Gensicke H, et al. MS quality of life, depression, and fatigue improve after mindfulness training: a randomized trial. Neurology. 2010;75(13):1141–1149.
9. Hanken K, Eling P, Hildebrandt H. Is there a cognitive signature for MS-related fatigue? Multiple Sclerosis Journal 2015, Vol.21(4)376-381
10. Hugos CL, Copperman LF, Fuller BE, Yadav V, Lovera J, Bourdette DN. Clinical trial of a formal group fatigue program in multiple sclerosis. Multiple Sclerosis. 2010;16(6):724–732.
11. Knoop H, van Kessel K& Moss-Morris R. Which cognitions and behaviors mediate the positive effect of cognitive behavioral therapy on fatigue in patients with multiple sclerosis? Psychological Medicine(2012),42,205-213
12. Mathiowetz VG, Finlayson ML, Matuska KM, Chen HY, Luo P. Randomized controlled trial of an energy conservation course for persons with multiple sclerosis. Multiple Sclerosis. 2005;11(5):592–601
13. Mohr DC, Hart SL, Goldberg A. Effects of treatment for depression on fatigue in multiple sclerosis. Psychosmotaci Medicine 65:542-547(2003).
14. Moss-Morris R, McCrone P, Yardley L, van Kessel K, Wills G, Dennison L. A pilot randomized controlled trial of an Internet-based cognitive behavioral therapy self-management programme (MS Invigor8) for multiple sclerosis fatigue. Behavior Research and Therapy 50(2012) 415-421.
15. Nasjonal kompetansetjeneste for multippel sklerose (MS) Norsk veileder om MS(2016): https:helse-bergen.no/norsk-ms-veileder
16. National Institute for Health and Care Excellence(NICE): Multiple sclerosis in adults: management. Clinical guideline [CG186] Published date: October 2014 Nasjonal kompetansetjeneste for multippel sklerose (MS) En norsk veileder om MS(2016): https:helse-bergen.no/norsk-ms-veileder
17. Packer TL, Brink N, Sauriol A. Managing fatigue: a six-week course for energy conservation. Tucson: Therapy skill builders;1995.
18. Penner IK, Raselli C, Stocklin M, Opwis K, Kappos L, Calabrese P. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. Multiple Sclerosis 2009;15:1509-17.
19. Thomas PW, Thomas S, Kersten P, Jones R, Slingsby V, Nock A, Smith AD, Baker R Galvin KT and Hiller C. One year foloow up of a pragmatic multi-centre randomized controlled trial of a group based fatigue management programme(FACETS) for people with multiple sclerosis. BMC Neurology 2014, 14:109
20. Thomas S, Thomas PW, Kersten P, Jones R, Green C, Nock A, Slingsby V, Smith AD, Baker R, Galvin KT, Hillier C. A pragmatic parallel arm multi-centre randomized controlled trial to assess the effectiveness and cost effectiveness of a group-based fatigue management programme(FACETS) for people with multiple sclerosis.J.Neurol Neurosurg Psychiatry 2013;84:1092-1099.
21. Thomas S, Thomas PW, Nock A, et al. Development and preliminary evaluation of a cognitive behavioral approach to fatigue management in people with multiple sclerosis. Patient Educ Couns 2010;78:240-9
22. van den Akker LE, Beckerman H, Collette EH, Twisk JWR, Bleijenberg G, Dekker J, Knoop H, de Groot V. Cognitive behavioral therapy positively affects fatigue n patients with multiple sclerosis: Results of a randomized controlled trial. Multiple Sclerosis Journal 2017, Vol.23(11)1542-1553.
23. van den Akker LE, Beckerman H, Collette EH, Eijssen ICJM, Dekker J, de Groot V. Effectiveness of cognitive behavioral therapy for the treatment of fatigue in patients with multiple sclerosis: A systematic review and meta-analysis. Journal of Psychosomatic Research 90(2016) 33-42.
24. van den Akker LE, Beckerman H, Collette EH, Knoop H, Bleijenberg G, Twisk JW, Dekker J, de Groot V, TREFAMS-ACE study group. Cognitive behavioral therapy for MS-related fatigue explained: A longitudinal mediation analysis. J Psychosom Res. 2018 Mar;106:13-24. doi: 10.1016/j.jpsychores.2017.12.014. Epub 2017 Dec 28
25. van Kessel K, Moss-Morris R. Understanding multiple sclerosis fatigue: A synthesis of biological and psychological factors. Journal of Psychosomatic Research 61(2006) 583-585.
26. van Kessel K, Moss-Morris R, Johnson M H. A randomized Controlled trial of Cognitive behavior Therapy for Multiple Sclerosis Fatigue. Psychosomatic Medicine 70:205-213(2008).
27. van Kessel K, Wouldes T, Moss-Morris R. A New Zealand pilot randomized controlled trial of a web-based interactive self-management programme(MSInvigor8) with and without email support for the treatment of multiple sclerosis fatigue. Clinical Rehabilitation 2016. Vol.30(5) 454-462.
28. Wendebourg MJ, Heesen C, Finlayson M, Meyer B, Pöttgen J, Köpke S. Patient education for people with multiple sclerosis-associated fatigue: A systematic review. PLoS One.2017;12(3): e0173025. Systematic review of the literature to determine the effect of patient education programs on fatigue in MS.