Methylphenidate for fatigue management in palliative care cancer patients: Who and how for benefit? A literature review

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Abstract

Background: Cancer-related fatigue (CRF) is a highly prevalent and challenging symptom to manage in patients with advanced cancer. Non-drug interventions, treating contributing medical conditions and courses of steroids are often insufficient. Updated National Comprehensive Cancer Network (NCCN) Guideline on the topic includes off-label psychostimulants for selected patients. The most studied CRF stimulant is the dopamine-and norepinephrine enhancing drug Methylphenidate (Mph). A 2016 meta-analysis found weak evidence of some benefit in general palliative cancer patients. Mph is used for CRF in USA, around Europe and in some Scandinavian centres. Norwegian palliative cancer care guideline does not address the subject.

Aims and objectives: To review the existing RCTs for evidence of patient characteristics and other factors associated with benefit of Mph to manage fatigue in palliative cancer patients.

***Methods*:** An electronic search of EMBASE, PubMed and PsycINFO was conducted from 2008 through 2017. Study selection criteria were adult palliative cancer patients (any cancer/stage/anti-cancer treatment), Mph compared to placebo and fatigue by PROM as primary outcome. Additional records were hand searched from relevant sources. Grey literature and published protocols were not searched. Selection process followed PRISMA flowchart procedure. Study quality was assessed by simplified Cochrane Risk of Bias tool + 4 added domains. Global evidence quality was rated by modified GRADE criteria. Both tools apply quality rating high – moderate – low – very low. Data were analysed qualitatively for narrative synthesis.

Results: 8 RCTs were selected, enrolling 691 participants of mean age 60 years, 62% females, 60% receiving some type of active tumour therapy. RCTs were small (24 to 190 participants) and diverse with respect to patient characteristics, exclusion criteria, measurement, baseline fatigue, Mph dose (5 to 50mg) and drug duration (2 to 10 weeks). 2 studies were rated as high and moderate quality, 5 studies as low and 1 study as very low quality, the main quality issues being unclear allocation concealment and high risk of attrition bias. 4 RCTs found improvement in placebo arm. 6 RCTs had significant fatigue reduction in Mph-arm compared to controls ($p<0,05$), over-all or in subsets. Improvements were clinically important. Palliative chemotherapy, far advanced disease, severe baseline fatigue, prostate cancer on androgen deprivation therapy (ADT), Mph dose above 5mg x 2 and treatment duration at least 3-4 weeks appear associated with Mph benefit. There was no obvious internal connection between required dose and the other factors. Adverse events were equal between arms up to 30 mg, nausea and insomnia most frequently reported. There were no serious adverse events. Global quality of evidence was rated "low", downgrading due to possible validity threats and imprecision.

Discussion: This review provides some guidance for selecting palliative CRF-sufferers most likely to benefit from Mph, though insufficient or lacking data on separate cancers and key factors like medication, sedation, performance status and nutritional status. CRF was measured by severity and interference, possibly losing multidimensional and diurnal variety perspective. Predictive value of severe baseline fatigue is supported by a 2011 study by Yennurajalingam et al, which also conclude on no association to baseline depression, anxiety or drowsiness. Placebo effects seen in several RCTs emphasize need for control groups in CRF-studies. Separation of placebo and Mph effect week 3-5 into intervention may explain shorter trials` failure to achieve significant differences. Regarding tolerability, low frequency and severity of adverse events are supported by several retrospective safety reviews. The limitations of this review are several. Only one person conducted selection, data extraction and quality assessment, studies are small and mostly seing CRF isolated from its symptom clusters, and literature search was not exhaustive thus reporting and publication bias not assessed.

Conclusion: There is low-quality evidence suggesting that Mph for CRF be reserved for the most severely fatigued and advanced cancer patients, fatigue sufferers recently having palliative chemo and ADT-treated men with prostate cancer. Life expectancy should be at least 4 weeks. There are no trials examining this intervention beyond 10 weeks. Mph appears safe up to 30mg/d, split in morning-and noon dosage. High quality RCTs of sufficient duration, targeting separate cancers and designed in more detail to determine benefit predictors are needed. Using tools sensitive to multidimensional CRF might add value.