Methylphenidate for the treatment of depressive symptoms, including fatigue and apathy, in medically ill older adults and terminally ill adults

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CRD summary
The review did not find definitive evidence of effectiveness of methylphenidate in medically ill older adults with depression, fatigue or apathy, although it appeared to be tolerated in the short term. Due to variation in outcomes, methodological flaws in the included studies and shortcomings in the review process, the reliability of the author's conclusions is not clear.

Authors' objectives
To assess the efficacy and tolerability of methylphenidate for the treatment of depressive symptoms, fatigue and apathy in medically ill older adults and adults receiving palliative care.

Searching
MEDLINE (from 1950), PsycINFO (from 1806), International Pharmaceutical Abstracts (from 1970) and the Cochrane Library were searched up to July 2008. Search terms were reported. Reference lists of retrieved studies were also searched.

Study selection
Systematic reviews, clinical trials and case series were eligible for inclusion if they evaluated methylphenidate for the treatment of depressive symptoms, fatigue or apathy in older adults (mostly aged ≥65 years), adults receiving palliative care or with terminal illness, or adults with other chronic illnesses. Chronic illnesses could include human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), stroke and traumatic brain injury. No other criteria for inclusion were specified. Studies of adults with bipolar disorder, attention-deficit hyperactivity disorder, narcolepsy, cataplexy, chronic fatigue syndrome and related disorders were excluded. Studies of adults with depression under the age of 65 without comorbid illness were also excluded.

In the included studies, participants mostly had chronic conditions with symptoms such as depression, fatigue and apathy. Chronic conditions included stroke, HIV, AIDS, and traumatic brain injury. A proportion of participants were receiving palliative care for terminal illness, mostly cancer. Patients were receiving rehabilitation, or living at home or with a family member, or hospitalised, or institutionalised. Doses of methylphenidate ranged from 2.5mg to 60mg per day; comparisons in controlled trials were mostly made against placebo. The review identified some of the measures used to score outcomes, including the Zung depression scale, the Hamilton Depression Rating Scale, Functional Independence Measure, Mini Mental State Examination and the Nurses Observation Scale, but for many studies no measurement scales were specified.

Outcomes included depressive symptoms, fatigue and apathy, but also included improvements in function, cognitive function, pain control, sleepiness, anger and social interaction.

The author did not state how studies were selected for the review.

Assessment of study quality
The author did not state that validity was assessed; however, randomisation, the level of blinding and type of control were noted in tables.

Data extraction
The author did not state how data were extracted for the review.

Methods of synthesis
The author described the studies in a narrative format in three broad groupings of participants: medically ill older
Results of the review
The review included 13 controlled trials, two prospective uncontrolled trials and 10 retrospective case series of medically ill older adults; six controlled trials, 11 prospective uncontrolled trials and two retrospective case series of adults with terminal illnesses or in palliative care; and 15 controlled studies and 11 case series of people with other chronic medical illnesses (numbers of participants were not specified for all studies). The authors noted that many studies of older adults had methodological flaws; studies of palliative care or other chronic conditions were of higher quality, but no details were provided on quality issues.

Controlled studies

Medically ill older adults: Six of ten controlled studies reported positive benefits for methylphenidate on at least one outcome.

Terminal illness and palliative care: Four of six double blind placebo-controlled randomised trials reported improved fatigue; two controlled trials reported improved cognition with methylphenidate in terminal illness and palliative care.

Adults with other chronic medical illnesses: Mixed results were reported for methylphenidate in people with HIV (five controlled studies) and traumatic brain injury (seven controlled studies).

Adverse events
Adverse events rates associated with methylphenidate ranged from 0 to 90%; most were considered mild. The most common adverse events included agitation or restlessness, sinus tachycardia or palpitations, delirium or confusion and insomnia. Two thirds of controlled studies found no significant differences in the prevalence of adverse events between methylphenidate and placebo.

The results of non-controlled studies were also reported.

Authors’ conclusions
In the absence of definitive evidence of effectiveness, trials of low dose methylphenidate in medically ill adults with depression, fatigue or apathy, with monitoring for response and adverse effects, are appropriate.

CRD commentary
The research question was clearly stated. Broad inclusion criteria were specified for study design and participants. However, insufficient details were provided for eligible outcomes and a wide range of outcomes were measured in the review. A number of electronic databases were searched and efforts were made to find additional studies by searching reference lists. The authors did not report whether they looked for unpublished studies or whether language restriction was applied, so publication and language bias could not be ruled out. The methods used for study selection and data extraction were not reported, so there was the possibility of reviewer error and bias.

Although the author did not state that a validity assessment was undertaken, some aspects of validity were noted in tables and it was acknowledged that many of the included studies had methodological flaws. As types of participants and outcomes varied widely, the results from the studies were reported appropriately in narrative format. The results section also contained details of other studies that did not meet the inclusion criteria. The authors reported the proportion of studies which reported positive effects for methylphenidate on any outcomes measured in three subgroups of participants, but because outcomes varied and studies with one participant were counted as equal to larger studies, it was difficult to reach conclusions on effectiveness.

The author’s conclusions reflected the broad evidence base, but given the wide variation in outcomes measured, methodological flaws in the included studies and potential shortcomings in the review process, the reliability of the conclusions is not clear.
Implications of the review for practice and research

Practice: The author stated that medically ill adults with depression, fatigue or apathy treated with methylphenidate should be monitored for response and adverse events.

Research: The author stated that a well designed randomised controlled trial of adequate power is needed, in which optimal dosing and duration of treatment is determined, to assess the efficacy and tolerability of methylphenidate in medically ill older adults.

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