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Methylphenidate for Treatment of Depressive Symptoms, Apathy, and Fatigue in Medically Ill Older Adults and Terminally Ill Adults

Susan E. Hardy, MD, PhD[*]

[*] University of Pittsburgh School of Medicine

Abstract

Background—Depressive symptoms, apathy, and fatigue are common symptoms among medically ill older adults and patients with advanced disease, and are associated with morbidity and mortality. Methylphenidate has been used to treat these symptoms because of its rapid effect.

Objective—To review the literature regarding the efficacy and safety of methylphenidate to treat depressive symptoms, apathy, and fatigue in medically ill older adults and in palliative care.

Methods—English-language articles presenting systematic reviews, clinical trials, or case series describing use of methylphenidate to treat depressive symptoms, fatigue, or apathy in medically ill older adults or in palliative care were identified. The keywords “methylphenidate” and either “depressive”, “depression”, “fatigue”, or “apathy” were used to search the Cochrane Database, MEDLINE, PsycINFO, and International Pharmaceutical Abstracts. Included articles addressed depressive symptoms, apathy, or fatigue in 1) older adults (generally age 65 years or older), particularly those with comorbid medical illness; 2) adult patients receiving palliative care; and 3) adults with other chronic illnesses. We excluded articles regarding 1) treatment of depression in healthy young adults; 2) treatment of bipolar disorder or attention-deficit hyperactivity disorder; and 3) treatment of narcolepsy, chronic fatigue syndrome and related disorders.

Results—19 controlled trials of methylphenidate in medically ill older adults or in palliative care were identified. Unfortunately, their conflicting results, small size, and poor methodologic quality limit our ability to draw inferences regarding the efficacy of methylphenidate, although the evidence of its safety is stronger. The available evidence suggests possible effectiveness of methylphenidate for depressive symptoms, fatigue, apathy, and cognitive slowing in various medically ill populations.

Conclusions—In the absence of definitive evidence of effectiveness, trials of low-dose methylphenidate in medically ill adults suffering from depression, apathy, or fatigue with monitoring for response and adverse effects are appropriate.

Keywords

methylphenidate; depression; apathy; fatigue; older adults; palliative care; medically ill

INTRODUCTION

Depressive symptoms, apathy, and fatigue are common symptoms among medically ill older adults and patients with advanced disease. A quarter of hospitalized older adults meet criteria for major depression.[1] Among patients with advanced disease receiving palliative care, the prevalence of major depression is approximately 15%, with clinically significant depressive

Corresponding Author: Susan Hardy, MD, PhD Division of Geriatric Medicine University of Pittsburgh 3471 Fifth Avenue, Suite 500 Pittsburgh, PA 15213 Phone: (412) 692−2360 Fax: (412) 692−2370 Email: hardys@dom.pitt.edu.

symptoms present in 30%.[2] Among acutely ill hospitalized older adults, depressive symptoms are associated with mortality, disability, and poor health status.[3, 4] An association between depressive symptoms and poor recovery has been reported in a variety of illnesses, including hip fracture and other injuries, acute myocardial infarction, and stroke.[5, 6] Depressive symptoms affect older adults ability to participate in rehabilitation and other aspects of their care, leading to adverse outcomes.[7-9]

Since their introduction in the 1930s, psychostimulants such as amphetamine and methylphenidate have been used in the treatment of depression. Methylphenidate, a piperadine derivative, is a central nervous system stimulant FDA-approved for treatment of attention deficit hyperactivity disorder and narcolepsy.[10] It is a chiral drug with four entantiomers; most clinical preparations contain both d- and l-threo entantiomers, although only the d-threo entantiomer is clinically active.[11] Dexmethylphenidate contains only the d-threo entantiomer and is twice as potent as standard methylphenidate at the same dose. Although methylphenidate's mechanism of action is not completely understood, it is known to bind to the dopamine transporter in the presynaptic cell membrane, blocking dopamine reuptake and increasing extracellular dopamine levels.[12] The highest area of methylphenidate uptake in humans is the striatum, where dopamine enhances the signal to noise ratio and increases salience of a stimulus and motivation for goal-directed behavior.[11] Methylphenidate also inhibits norepinephrine reuptake and (weakly) serotonin reuptake.[13]

While the use of methylphenidate in depression declined with the introduction of tricyclic antidepressants in the 1950s and selective serotonin reuptake inhibitors in the 1980s, interest in methylphenidate as an antidepressant has persisted, particularly in the settings of medical illness and palliative care.[12] The rapid onset is particularly attractive in these settings. Despite the long history of methylphenidate use in the treatment of depressive symptoms, fatigue, and apathy, there is little definitive evidence to support its use. We review the literature regarding the efficacy and safety of methylphenidate to treat these symptoms in medically ill older adults and in patients receiving palliative care.

MATERIALS AND METHODS

Data Sources

English-language articles presenting systematic reviews, clinical trials, or case series describing use of methylphenidate to treat depressive symptoms, fatigue, or apathy in medically ill older adults or in the palliative care setting were identified. The first step in data collection was a search in the Cochrane Database of Systematic Reviews (through 2008 Issue 3) using the keywords “methylphenidate” and either “depressive”, “depression”, “fatigue”, or “apathy”. These search terms were also used to identify individual articles in MEDLINE (1950 to July 2008), PsycINFO (1806 to July 2008) and International Pharmaceutical Abstracts (1970 to July 2008). The references of all pertinent articles (including review articles) were also searched for eligible articles.

Selection Criteria

Articles were included if they addressed depressive symptoms, apathy, or fatigue in 1) older adults (defined as age 65 years or older, although some articles with lower age cutoffs were included), particularly those with comorbid medical illness; 2) adult patients receiving palliative care or with terminal illness; and 3) in adult patients with other chronic medical illnesses. We excluded articles regarding 1) treatment of depression in adults younger than 65 without comorbid illness; 2) treatment of bipolar disorder or attention-deficit hyperactivity disorder; and 3) treatment of narcolepsy, cataplexy, chronic fatigue syndrome and related disorders. We also excluded articles assessing psychological response to methylphenidate in

healthy adults or other non-clinical populations. Because of the relative paucity of evidence, we examine case series and case reports in addition to controlled trials.

RESULTS

Systematic Reviews

Two recent Cochrane reviews have addressed the use of psychostimulants for depression[14] and pharmacologic treatment for cancer-related fatigue.[15] The review of psychostimulants for depression was limited to randomized controlled trials and identified only 24 trials, 10 of which involved methylphenidate. They report that the trials were small and of poor quality, and conclude that "few clinically relevant conclusion can be drawn." Six of these trials were studies of younger outpatients without major medical comorbidity, and thus were not included in this review. The two trials with more than 100 participants showed positive effects of methylphenidate,[16, 17] while the other four, all with 60 or fewer participants, showed no significant difference between methylphenidate and placebo.{Mattes, 1985 #3101; Patkar, 2006 #3102; Robin, 1958 #3103; Postolache, 1999 #3027} Three positive studies are described later in this review.{Fernandez, 1995 #2942; Lee, 2005 #2985; Wallace, 1995 #3052} The final study found that a single dose of intravenous methylphenidate improved mood in depressed patients without Parkinson's disease, but not in those with Parkinson's disease. {Cantello, 1989 #3104} Overall, these studies leave a mixed picture of the potential role of methylphenidate in depression treatment, with more positive results in older adults and the chronically ill. Two randomized controlled trials of methylphenidate[18, 19] were included in the cancer-related fatigue review and are described below (Table 2). Combining the trials they found evidence that methylphenidate was significantly better than placebo for the treatment of cancer-related fatigue.

Controlled Trials

Medically Ill Older Adults—The characteristics of the 13 controlled trials evaluating the use of methylphenidate in medically ill older adults are presented in Table 1.[20-32] All of the trials were small (between 1 and 70 participants) and compared methyphenidate with placebo. Seven trials, [20, 22, 24, 27, 29, 30, 32] including two "N-of-1" trials,[27, 29] were crossover trials and six[21, 23, 25, 26, 28, 31] were parallel comparisons. Most of the trials provide limited methodologic details, limiting our ability to assess the validity of the individual trials. Of the 11 trials[20-24, 26-28, 30, 32] in which statistical significance was evaluated (or could be calculated from data provided), seven[23, 24, 26-28, 30, 32] reported positive results for at least one outcome. Studies specifically measuring depressive symptoms or apathy[23, 24, 26-28, 30-32] were more likely to be positive (7/8) than those measuring other outcomes[20-22] (0/3).

In addition to using methylphenidate as monotherapy, several more recent studies have used methylphenidate in combination with a standard antidepressant to accelerate or enhance the response to the standard agent. Cases reporting the effectiveness of methylphenidate in achieving therapeutic response in patients with inadequate response to standard antidepressants, have been in the literature since the 1960s.[33-36] After two prospective uncontrolled trials of older adults (aged 70 years or older) showing response to the combination of citalopram and methylphenidate within 2 weeks in a majority of patients,[37, 38] a small randomized, double-blind trial comparing citalopram and methylphenidate to citalopram and placebo found responses (defined as a Hamilton Depression Rating Scale score less than 10) in 5/6 patients receiving methylphenidate compared to 0/6 receiving placebo (p=0.04).[39] However, a controlled trial of sertraline and methylphenidate in younger adults found no benefit.[40]

Terminal Illness and Palliative Care—Methylphenidate has been used in palliative care to treat fatigue, depression and opiate-associated sedation, to potentiate the analgesic effect of opiates, and to improve cognitive function.[10, 41, 42] The characteristics of the 6 controlled trials evaluating the use of methylphenidate in terminal illness and palliative care are presented in Table 2.[18, 19, 43-46] Methylphenidate improved fatigue in 4/6 studies[19, 43, 44, 46] and cognition in 2/2 studies. [44Lower, 2005 #2989]

Other Chronic Medical Illnesses—Methylphenidate has been used as a treatment for depression, cognitive symptoms, and fatigue in a wide variety of chronic medical conditions, including HIV and AIDS, stroke, and traumatic brain injury.[47] Studies of methyphenidate in HIV patients have mixed results, but generally suggest some benefit for depressive symptoms (2 of 3 studies),[48-50] fatigue (1 of 1 study),[51] and cognitive deficits (2 of 3, with the third suggesting benefit in the subgroup with the greatest impairment).[49, 50, 52] Studies of methylphenidate in traumatic brain injury suggest benefit for cognition, particularly attention, (4 of 6 studies),[53-58] but not for behavioral symptoms (2 of 6 studies).[53, 55-59] Studies suggest a beneficial effect of methylphenidate on fatigue associated with Parkinson's disease,[60] sarcoidosis,[61] and possibly α-interferon treatment.[62]

Case Series and Case Studies

Medically Ill Older Adults—The characteristics of 2 prospective uncontrolled trials[63, 64] and 9 retrospective complete case series[65-74] of medically ill older adults treated with methylphenidate are presented in Table 3. A prospective trial of 10 post-stroke rehabilitation patients with major depression reported a response rate of 40%,[63] while the retrospective series reported response rates between 33% and 83% for depressive disorders.[65-74] One series of medically ill adults reported response rates overall[71] and in those aged 65 years or older;[72] response rates among older adults (n=25) were lower than for younger adults (n=19), although this result was not statistically significant (89% versus 68%, p=0.15). A prospective trial of methylphenidate for negative symptoms such as anhedonia and psychomotor retardation in patients with Alzheimer's disease or vascular dementia[64] reported significant improvement in symptoms scores, but did not provide response rates. Reports of successful uses of methylphenidate in the literature include treatment of lethargy and depressive symptoms in mechanically ventilated patients who are difficult to wean,[75, 76] treatment of anorexia in apathetic, severely demented nursing home residents,[77], and treatment of depressive symptoms in patients up to 106 years of age.[78]

Terminal Illness and Palliative Care—The characteristics of 11 prospective uncontrolled trials[44, 79-88] and 2 retrospective complete case series[89, 90] of palliative care patients treated with methylphenidate are presented in Table 4. Among patients with depressive disorders, response rates ranged from 73% to 81%[81, 84, 89, 90] except in a study of hospice inpatients by Macleod with a 27% response rate.[85] Macleod noted that 54% of the patients in his study died within 6 weeks, and that only one of these patients response, suggesting that methylphenidate may not be effective or may require higher doses in the last weeks of life. Response rates for opiate-induced somnolence or sedation ranged from 80% to 88%,[44, 79] and for fatigue from 38% to 82%.[80, 83, 88] Two studies demonstrated significant improvements in cognitive function.[82, 86] Methylphenidate has been succesully used to treat hypoactive delirium in the terminally ill in several case reports.[91, 92]

Other Chronic Medical Illnesses—There are numerous cases in the literature reporting successful use of methylphenidate for depression and cognitive symptoms in HIV/AIDS,[93, 94] intensive care patients with respiratory failure,[95, 96] and other chronic illnesses.[97-99] Cases of apathy independent of depression successfully treated with methylphenidate are also reported.[100-103]

Guidelines/Treatment Algorithms

Methylphenidate is recommended as a potential treatment in guidelines or treatment algorithms for major depression in advanced cancer,[104-106] augmentation therapy in geriatric depression,[107] and neurobehavioral sequelae of traumatic brain injury.[108] In their treatment algorithm for depression in advanced cancer,{Nakano, 1999 #3009; Okamura, 2008 #3013} Nakano and colleagues recommend methyphenidate alone or in combination with other drugs, particularly for older patients experiencing lethargy or fatigue. They base this recommendation on a single RCT{Wallace, 1995 #3052} and several uncontrolled studies. Passik and colleagues{Passik, 2002 #3019} describe successful implementation of a treatment algorithm in oncology clinics which recommended fluoxetine in combination with methylphenidate for depressed patients with prominent fatigue. Oshima and Higuchi{Oshima, 1999 #3016} recommend methylphenidate as augmentation therapy in geriatric major depression, based on observational studies. These algorithms and recommendations for methylphenidate use in depression are based on relatively weak evidence. In a thorough and evidence-based guideline for the treatment of neurobehavioral sequellae of traumatic brain injury,{Neurobehavioral Guidelines Working Group, 2006 #3011} the Neurobehavioral Guidelines Working Group recommended methylphenidate for the treatment of deficits in attention and processing speed based on two well-designed randomized controlled trials, three prospective studies, and three retrospective studies.

Tolerability and Adverse Reactions

Most studies suggest that methylphenidate is well tolerated in the medically ill, the terminally ill, and older adults (see Tables 1-4). Adverse effects occur in 0% to 90% of patients on methylphenidate, with the majority of studies reporting rates between 5% and 30%; most adverse effects are mild and resolve with discontinuation of therapy. Most controlled studies showed no difference in adverse events between methylphenidate and placebo.[18, 20-23, 28, 30-32, 43, 45, 46, 55-58, 60, 61, 109] Herrmann and colleagues[24] reported significantly more adverse effects on methylphenidate versus placebo in patients with apathy in Alzheimer's disease, with two patients developing severe delirium. Lower and colleagues[19] found high rates of adverse events in cancer patients taking either methylphenidate or placebo (90% versus 78%, p=0.08); nausea, dry mouth, dizziness, and jitteriness were more common in the methylphenidate group. Breitbart and colleagues[51] found that AIDS patients receiving methylphenidate experienced significantly more adverse effects than those receiving placebo, particularly hyperactivity or jitteriness. In patients receiving methylphenidate, adverse effects were no more frequent than in patients receiving desipramine[48] or nortriptyline[68], and were less frequent than in patients receiving sertraline.[54] While standard antidepressants have been associated with increased risk of falls,[110, 111] older adults improved in mobility, gait variability, and executive function after a single dose of 20mg of methylphenidate.[112]

The most common adverse effects reported are agitation or restlessness, sinus tachycardia or palpitations, delirium or confusion, and insomnia. Both hypertension and hypotension have been reported in older adults on methylphenidate, although both are relatively infrequent. One serious but uncommon adverse effect was arrhythmia,[65, 113-115] which was reversible with discontinuation in all cases. Cases have been published reporting multiple strokes in a 63 year old woman treated for hyperactivity with methylphenidate,[116] and auto-immune hepatitis in a 57 year old liver transplant patient which resolved after methylphenidate was discontinued.[117] Two case series of patients taking methylphenidate for 12 to 54 months found no evidence of adverse effects or development of dependence.[99, 118] Steibel[119] reports two cases of patients with end stage renal disease treated with methylphenidate with no evidence of clinical toxicity or elevated drug levels. Two case series of adult epilepsy patients and brain injured patients with seizure disorders showed no increase in seizure rates with methylphenidate treatment.[120, 121]

In 2007, the FDA required new warnings in psychostimulant labeling regarding reports of serious cardiovascular events, including sudden death, stroke, and myocardial infarction in children and adults using stimulants for attention deficit hyperactivity disorder. A comprehensive review of clinical data on over 500,000 individuals prescribed psychostimulants is currently underway.{, #3105} Between 1992 and 2004, sudden death was reported to the FDA in 2 adults and 11 children taking methylphenidate. Over a five year period from 1999 to 2003, there were 11 spontaneous reports of serious nonfatal cardiovascular or cerebrovascular adverse events in adults taking methylphenidate, including syncope, hypertension, chest pain, heart failure, myocardial infarction, arrhythmia, mitral valve prolapse, and stroke.{, #3107} In a six-week study of adults aged 19 to 60 years with attention deficit hyperactivity disorder treated with an average of 1.1 mg/kg/day of methylphenidate, close clinical monitoring including electrocardiography revealed small but statistically significant increases in pulse (7 beats per minute, $p < .001$), but not in systolic or diastolic blood pressure (both increased 2mm Hg, $p=.10$ and $p=0.6$ respectively). On electrocardiography, there were slight increases in ventricular rate (7 beats per minute, $p<.001$) and QTc interval(. 007s, $p<.01$). There were no symptoms or adverse events referable to the cardiovascular system.{Spencer, 2005 #3106} While these were relatively young and healthy patients, the average dose (82 ± 22 mg/day) was much higher than the maximum dose I would recommend for older adults (20 mg/day). In a study of fatigued geriatric rehabilitation patients, heart rate increased 5−10% with methylphenidate doses of 20mg/day and was unchanged with placebo. {Larsson, 1988 #2979} Among the 24 participants in this study, 10 had pacemakers or were taking a beta-blocker or digoxin and none experienced cardiovascular side effects. Among the 31 patients aged 65 and older who received methylphenidate augmentation in Lavretsky and colleagues studies,{Lavretsky, 2003 #2980; Lavretsky, 2001 #2982; Lavretsky, 2006 #2981} only one subject experienced a fluctuation of greater than 10% in heart rate or blood pressure, and this responded to dosage adjustments of his antihypertensives. These studies included participants with hypertension, coronary artery disease, and cerebrovascular disease.

In medical illness and palliative care, malnutrition and weight loss are often major problems. An anorexigenic effect of methylphenidate would limit its usefulness in these populations. Several early trials of methylphenidate in institutionalized chronically-ill older adults reported stable weights compared to placebo on doses of 20−60mg per day for 4−8 weeks.[21, 22, 28] In a trial of methylphenidate for cancer-related fatigue, self-rated appetite improved in both the methylphenidate and placebo groups (with no significant difference between them), and appetite improved significantly from baseline for the methylphenidate group.[18] In a trial of methylphenidate for HIV-associated depression, patients taking methylphenidate were more likely to report weight loss than those taking desipramine (2/8 versus 0/12, $p=0.14$). Maletta and colleagues report three cases of methylphenidate used to reverse anorexia in apathetic, severely demented nursing home patients; in all three cases weight loss stabilized or reversed and no changes in blood pressure or evidence of delirium occurred.[77] Among 25 medical and surgical inpatients treated with methylphenidate, no anorexia was observed and appetite improved in many patients.[72]

Drug-Drug Interactions—Methylphenidate should not be used in patients receiving monoamine oxidase inhibitors due to risk of hypertensive crisis and serotonin syndrome, although there are case reports of successful concomitant use.[122] Although in vitro studies have shown increased levels of tricyclic antidepressants when administered with methylphenidate, [123] an observational study in children showed no significant interaction between methylphenidate and despiramine levels.[124] In healthy adults, administration of quinidine, a potent cytochrome P450 2D6 inhibitor, with methylphenidate had no effect on the pharmacokinetics of methylphenidate or its metabolites, suggesting that tricyclic antidepressants and other P450 2D6 inhibitors should not interact with methylphenidate.[125] However, caution should still be used when combining methylphenidate and tricyclic

antidepressants. Perhaps because selective serotonin reuptake inhibitors are metabolized in the liver while 80% of methylphenidate is metabolized extrahepatically, there are no reports of interactions for the combination.[123] Methylphenidate has been reported to inhibit the metabolism of some antidepressants,[123] while anticonvulsants have been reported to decrease the effectiveness of methylphenidate secondary to induction of cytochrome P450 3A4-mediated methylphenidate metabolism.[126] Overall, administration of methylphenidate with anticonvulsants appears safe with careful monitoring.[127] Methylphenidate may also increase warfarin levels through inhibition of warfarin metabolism.[126]

DISCUSSION

Despite the long history of methylphenidate use in older adults and the medically ill, the data to support such use is of relatively poor quality. None of the clinical trials in older adults had more than 70 participants, and many, particularly those published before the CONSORT guidelines were adopted, had substantial methodologic flaws. Controlled trials in palliative care, HIV/AIDS, stroke, and traumatic brain injury are more recent and tended to be of higher quality, but still gave mixed results. The weight of the evidence suggests possible effectiveness of methylphenidate for depressive symptoms, fatigue, apathy, and cognitive slowing in a variety of medically ill populations. Strong evidence of effectiveness would require a well designed randomized, controlled trial with adequate power.

Evidence for the safety of methylphenidate in the medically ill is considerably stronger than for effectiveness. Evidence from both controlled clinical trials and the extensive case series that have been published indicate a very low risk of serious adverse effects. Although a causal link has not been determined, there have been reports of sudden unexplained death, stroke, and myocardial infarction in adults receiving usual dosages of stimulants for the treatment of ADHD.[126] No published reports of deaths attributable to methylphenidate in adults were identified. Methylphenidate appears to be at least as safe and well tolerated as standard antidepressants in the medically ill.

Given the safety of methylphenidate, trials of methylphenidate in medically ill adults suffering from depression, apathy, or fatigue with monitoring for response and adverse effects are appropriate. I would recommend initial dosing of 5mg methylphenidate with breakfast, or 2.5mg in patients who are frail or have significant cardiovascular disease, increasing by 2.5−5mg every one to two days in divided doses at breakfast and lunch if well tolerated and not effective to a maximum dose of 20−30mg/day. If ineffective after three days on the maximum dose, methylphenidate should be tapered and discontinued. Blood pressure and pulse should be monitored before and during methylphenidate therapy. It would be prudent to monitor the INR or drug levels in patients receiving warfarin or anticonvulsants. The optimal duration of therapy in patients who respond to methylphenidate is unclear. In patients with acute or subacute illness, the medication can be tapered once the condition has stabilized. While most studies have demonstrated little evidence of habituation to the effects of methylphenidate, it is possible that doses may need to be increased in long-term therapy to maintain effectiveness.

CONCLUSIONS

Depressive symptoms, fatigue, and apathy are common symptoms among medically ill older adults, patients receiving palliative care, and chronically ill adults. Methylphenidate has long been used in these populations because of its benign adverse effect profile and the rapid response to treatment. In the absence of definitive evidence of effectiveness, trials of methylphenidate in medically ill adults suffering from depression, apathy, or fatigue with monitoring for response and adverse effects are appropriate.

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Table 1

Controlled trials of methylphenidate in medically ill older adults.

Author, Year	N	Age	Population	Diagnoses	Design	Intervention	Results	Adverse Effects
Dube, 1956	20	51−90, mean 72	variety of chronic illnesses	senility	double-blind crossover trial	4-week blocks of MP 10mg QID, Reserpine (R) .25mg QID, and P	Number of 20 improved in physical state (MP 4, PB 2, R 2), mental state (MP 11, PB 6, R 6), and progress in rehabilitation (MP 6, PB 1, R 2). Not statistically significant.	irritability in 1 patient
Jacobson, 1958	54	60−74	outpatients, some with chronic disease	depression (no history of mania)	non-randomized (alternating assignment), single-blind (patients)	MP 10−30 mg/d vs P	Response MP vs. P: Good: 37% vs. 15% Partial: 44% vs 26% (overall p=.008)	insomnia (late afternoon dose); no nausea, vomiting, or hypertension
Landman, 1958	61	mean 71	debilitated chronic care hospital patients	lethargy, fatigue and emotional depression	double-blind crossover trial	10mg TID vs P	Response MP vs placebo: Marked 61% Possible or none 39% (p=0.005)	2 patients: slight tremor, insomnia; no effect on pulse or blood pressure
Darvill, 1959	70	65−98	cognitively impaired, institutionalized	senile	double-blind parallel trial	of MP 30 −60mg/d for 8 weeks versus P	no improvement in behavior with MP	no difference in adverse events in MP versus P
Holliday, 1965	na	"aged"	Schizophrenia, Organic brain syndrome	apathy and anergy	double-blind parallel trial	MP 20mg vs, protryptyline 20 mg vs placebo × 16 wks	Overall no difference; positive effect of MP vs P in organic brain syndrome but not schizophrenia (numeric results na)	na
Kaplitz, 1975	44	61−95; mean 78	chronic disease hospital patients	withdrawala nd apathy	randomized, double-blind parallel trial	MP 10mg BID vs placebo × 6 wks	Mental status checklist: MP better, p=.01 Nurses Observation Scale: MP better, p=.01	none reported by patients or nurses, no weight changes
Crook, 1977	12	mean 72	living with family member in community	cognitive impairment	double-blind crossover trial	MP 10mg vs MP 30mg vs P as single dose prior to testing	No significant improvement in cognitive measures with MP vs P	no AE; heart rate and blood pressure stable

Author, Year	N	Age	Population	Diagnoses	Design	Intervention	Results	Adverse Effects
Larsson, 1988	24	70–93	rehabilitation patients after medical illness	decreased interest in rehabilitation	double-blind parallel trial	MP 10–20mg/d in divided doses versus P	no difference between MP and P in psychological symptoms	none reported, heart rate and blood pressure increased in MP group at 20mg/d
Wallace, 1995	16	mean 72	medically ill inpatient or chronically ill homebound patients	Major depression (DSM-III-R)	randomized double-blind crossover trial	MP 5mg BID × 2 d then 10mg BID × 2d vs P	Hamilton scores improved more with MP than P ($p<0.05$)	no change in MMSE or vital signs; 1 patient "nervousness"
Grade, 1998	21	mean 71	post-stroke rehab pts	none	randomized, double-blind	MP 10–30mg (mean 22mg) BID vs P × 3wks	MP vs P: lower scores in 2 depression scales ($p=0.03$, 0.06), 2 functional measures ($p=0.03$, 0.08); no difference in cognition ($p=0.53$)	no patients withdrew due to AE; no difference in AE number ($p=0.94$)
Jansen, 2001	5	76–81		Depression in medical illness; Treatment-resistant depression; apathy in dementia	5 N-of-1 double-blind crossover trials, randomized treatment order	5 cycles of MP 5mg BID × 2d vs P × 2d, with 1d washout between treatments and 2d between cycles	depression: medical illness depression scores better on MP ($p=.09$, $p=.001$), treatment resistant score worsened on MP ($p=.09$) apathy: 1 improved ($p=.08$), 1 mutism (had severe dementia)	no change in functional status, no AE reported
Keenan, 2005	1	70	normal-pressure hydrocephalus	apathy; cognitive deficits	double-blind N-of-1 crossover trial	MP 20–40mg in single doses 2 hours prior to evaluation vs P	improvement in apathy on both MP doses vs P; in motivation, excitement, and energy MP 40mg vs P; improvement in 1 of 3 cognitive tests MP vs P	hypertension on 40mg dose; none on 20mg dose
Herrmann, 2008	13	mean 78	Alzheimer's disease	apathy	randomized, double blind crossover trial	MP 10mg BID versus P × 2 wks	greater improvement in apathy symptoms with MP than placebo ($p=0.047$)	AE on MP vs P 3 vs 1 ($p=0.038$); delirium/psychosis in 2 on MP

MP: methylphenidate; P placebo; BID: twice a day; TID: three times per day; QID: four times per day; na: not available; AE: adverse effects; DSM III-R: Diagnostic and Statistical Manual of Mental Disorders III, Revised

Table 2

Controlled trials of methylphenidate in terminal illness and palliative care

Author, Year	N	Age	Population	Diagnoses	Design	Intervention	Results	Adverse Effects
Bruera, 1987	32	mean 53	chronic pain in advanced cancer	opiate-induced sedation	randomized, double-blind crossover trial	MP 15mg/day vs P	MP group had better pain control (p<.02), activity (p<.05), and sleepiness(p<.02); 20/28 evaluable patients blindly chose MP as better treatment (p<.02)	rates of AE similar in MP and P; none required discontinuation
Bruera, 1992	20		cancer patients receiving continuous subcutaneous opiates	opiate-induced neuropsychological deficits	randomized, double-blind crossover trial	MP 10mg/d vs P	neuropsychological test performance and drowsiness symptoms better on MP (all p<0.01); 65% of patients and 70% of physicians blindly selected MP as more effective	AE in 1 (5%) on MP: confusion requiring discontinuation
Wilwerding, 1995	43	43−78, median 65	cancer pain on high-dose opiates (≥80mg/d oral morphine or equivalent)	pain control and opiate-induced toxicity	randomized, double-blind crossover trial	MP 10−15mg/d × 5d vs P × 5d	significant carryover effects limit interpretation; less drowsiness in MP vs P (p=0.01)	no differences in AE between groups
Lower, 2005	152	mean 53	cancer patients >2 mos after chemotherapy	fatigue, no other depressive symptoms	randomized, double-blind parallel trial	d-MP10−50mg/d (mean 25.5mg/d) versus P	d-MP vs P: improvement in fatigue and cognition (both p<0.05)	no serious AE; nausea, dry mouth, dizziness, jitteriness more common in d-MP group (p<0.05)
Bruera, 2006	112	22−85, median 56	cancer patients with hgb≥10	fatigue for ≥4d, with severity ≥ 4/10	randomized, double-blind parallel trial	MP 5mg q2h as needed for fatigue (max 20mg/d) vs P × 7 d (mean number of doses per day 2.3 MP, 2.1 P)	both groups had significant decrease in fatigue assessed with two different scales (all p<001); no significant difference between MP and P (p=.31 and p=.14)	no difference in AE between groups; no d-MP patients withdrew due to AE
Butler, 2007	68	28−83	patients receiving radiation for brain tumors	fatigue	randomized, double-blind parallel trial	d-MP 5−15mg BID versus P	no difference in fatigue at completion of radiation therapy or during the subsequent 12 weeks (p=0.64)	AE: 9% in d-MP and 3% in placebo; MP patients experience nausea and vomiting (2), and elevated liver enzymes (1)

MP: methylphenidate; d-MP: dexmethylphenidate; P placebo; BID: twice a day; hgb: hemoglobin; na: not available; AE: adverse effects

Table 3

Prospective uncontrolled trials and retrospective complete case series: medically ill older adults

Author, Year	N	Age	Population	Diagnoses	Design	Treatments	Results	Adverse Effects
Askinazi, 1986	13	58−89	medically ill rehabilitation inpatients	depression	retrospective	2.5−20mg/d daily to BID, duration 2−21d	Response: 3 (23%) marked, 2 (15%) moderate improvement, 2 (15%) mild, 6 (46%) none	AE in 2 (15%): rash, ventricular ectopy
Woods, 1986	36	37−87, mean 72	medically ill, hospitalized	depressive disorders	retrospective	5−30mg/d, mean 13.6mg/d	Response: 19% marked, 33% moderate, 25% minimal, 22% none; 93% of responses within 2d	stopped therapy in 7%: increased confusion in dementia, nausea, rash, sinus tachycardia
Masand, 1991	6	59−70	post-stroke (2wks-10yrs), hospitalized	depression	retrospective	5−15 mg/day	Response: 0 marked, 2 (33%) moderate, 3 (50%) minimal, 1 (17%) none	AE in 1 (17%): agitation
Masand, 1991	44	18−88, mean 65	medically ill, hospitalized	depressive disorders	retrospective	5−30 mg/d, mean 11mg/day	Response: 14 (32%) marked, 20 (45%) moderate, 4 (9%) minimal, 6 (14%) none; all responses within 4d	AE in 6 (14%): agitation (2), confusion, dizziness, hypertension, sinus tachycardia
Subset Age≥65 Pickett, 1990	25	65−88, mean 74	medically ill, hospitalized	depressive disorders	retrospective	5−20mg/d, mean 9mg/d	Response: 10 (40%) marked, 7 (28%) moderate, 3 (12%) minimal, 5 (20%) none; all responses within 4d	AE in 4 (16%): agitation, confusion, hypertension, sinus tachycardia
Rosenberg, 1991	29	23−85, mean 65	medically ill, hospitalized	depressive disorders	retrospective	5−30mg/d, mean 14.6mg	16 (55%) marked or moderate response; all responses within 2d of reaching maximal dose	AE in 8 (28%), discontinuation required in 5: tachycardia or hypertension (3), agitated or irritable (4), hallucinations
Johnson, 1992	10	64−83	Post-stroke rehabilitation	depression	retrospective	5−30mg/d, duration 5−30d	Response: 7 (70%) improved, 2 (20%) no change, 1 (10%) stopped for agitation; all responses within 4 days	AE in 3 (30%), discontinuation required in 1: insomnia (2), agitation
Kraus, 1992	6	58−79	medically ill, hospitalized	depressive symptoms	retrospective	10−30mg/d, divided BID to TID	Response: 3(50%) marked, 2 (33%) moderate, 1 (17%) minimal	well tolerated; some insomnia

Author, Year	N	Age	Population	Diagnoses	Design	Treatments	Results	Adverse Effects
Lazarus, 1992	10	mean 73.2	post-stroke rehabilitation	major depression by DSM III R criteria and HAM-D ≥ 18	prospective	2.5−5mg BID titrated to max of 40mg/day, mean dose 17mg/day	4 (40%) with ≥ 50% decrease in HAM-D score; 4 (40%) with 25−50% decrease in HAM-D score	AE (any new symptom) in 5 (50%), discontinuation required in 0: dyspnea, hypertension (2), restlessness, nausea (2), insomnia, irritability, orthostatic hypotension (2); no ECG changes
Lazarus, 1994	28	mean 73.7	hospitalized older adults; stroke within prior 2 years	major depression by DSM III R criteria	retrospective	≥10mg/d × ≥5d; mean 26mg/d, mean duration 14d; compared to 30 patients treated with nortriptyline	Response: 15(53%) complete resolution; mean time to response 2.4d; remission rate similar to that for nortriptiline (43%), response more rapid with MP (24−78 hrs vs 27d)	AE in 4 (14%): irregular heartbeat, tachycardia, agitation, visual hallucinations; fewer AE for MP vs nortriptyline (30%)
Galynker, 1997	27	62−92	Alzheimer's or vascular dementia	negative symptoms (anhedonia, psychomotor retardation)	prospective	MP 5−20mg/d daily to BID	improvement over 3−14 days in negative symptoms and HAM-D scores (all p<0.001)	AE in 2 (7%): agitation
Mantani, 2008	11	mean 73	cerebral infarction on MRI	major depression, failed standard therapies	retrospective	MP 5−20 mg/d, mean 9 mg/d × 4 wks	9/11 (82%) responded, (improvement of ≥50% on the HAM-D)	no severe adverse reactions

MP: methylphenidate; BID: twice a day; TID: three times a day; AE: adverse effects; DSM III-R: Diagnostic and Statistical Manual of Mental Disorders III, Revised; HAM-D: Hamilton Depression Rating Scale

Table 4

Prospective uncontrolled trials and retrospective complete case series: terminal illness and palliative care

Author, Year	N	Age	Population	Diagnoses	Design	Treatments	Results	Adverse Effects
Natenshon, 1956	26	n.a.	"incurables" including cancer	depressive symptoms	retrospective	up to 60mg/d	Response: 21 (81%) excellent; 3 (12%) good; 2 (8%) poor	AE in 2 (8%): insomnia (2)
Fernandez, 1987	30	30 to > 80; median 40−59	cancer	major depression or other disorders with depressed mood by DSM-III	prospective	MP 10mg TID, titrated if needed to a maximum of 80mg/day, maximum dose maintained for 1wk, then tapered if tolerated	Response: 23 (77%) marked or moderate; 4 (13%) minimal; 3 (10%) none; all responses within 4d; 11 patients had recurrent symptoms when tapered, maintained long term with good response	AE in 7 (23%); discontinuation and resumption at lower dose in 2: tachycardia with chest pain, confusion, agitation, palpitations, nausea, constipation, blood pressure and pulse changes
Bruera, 1989	50	mean 56	advanced cancer with pain on oral opiates	severe opiate-associated somnolence	prospective	MP 10mg BID	44 (88%) improved somnolence; 4 no response at 48 hours; 2 discontinued for adverse effects	AE requiring discontinuation in 2 (4%) for psychotic symptoms; all patients with anxiety or nervousness responded to decreased dose
Bruera, 1992	15	mean 63	cancer pain, majority from bone metastases	opiate-induced sedation	prospective	15mg/d divided BID, titrated as tolerated for symptom control; mean final dose 42mg/d	Response at 48hrs: 12 (80%) felt better; improvement in pain and sedation ratings ($p<0.01$); increase in tolerated opiate dose ($p<0.01$)	AE in 1 requiring discontinuation: acute dysphoria and agitation; mild AE: restlessness (6), sweating (4)
Olin, 1996	15	30−85	hospitalized cancer patients	depressive disorders	retrospective	5−30mg/d, average 8mg/d	Response: 4 (27%) marked, 8 (53%) moderate, 1 (7%) minimal, 2 (13%) none; most responses within 72 hrs	AE in 3 (20%): sinus tachycardia, agitation, confusion
Macleod, 1998	26	42−79, mean 64	inpatient hospice	depression	prospective	5−20mg/d	Response: 4 (15%) marked, 3 (12%) moderate, 5 (19%) minimal, 14 (54%) none	AE in 2 (8%), 1 required discontinuation: tachycardia, acute delirium

Author, Year	N	Age	Population	Diagnoses	Design	Treatments	Results	Adverse Effects
Meyers, 1998	30	15−70, mean 40	malignant glioma	neurobehavioral slowing affecting function	prospective	MP 5mg BID titrated to response, AE, or a max of 30mg BID	significant improvements in all neuropsychiatric tests from baseline; 78% reported subjective improvement at 10mg BID, and 100% at 30mg BID	AE in 2 (14%): irritability, shakiness
Homsi, 2001	41	30−90, mean 68	advanced cancer	depression	prospective	10−20mg/d, divided BID	30 (73%) improved, 70% of responses within 3d; 3 withdrew, 1 withdrew due to no response, 1 hospitalized and med stopped, 6 withdrawn for AE	AE in 13 (32%), 6 required discontinuation: agitation + insomnia (2), agitation (2), dysphoria, nightmares, nausea (2), insomnia, dry mouth (2), anorexia
Sarhill, 2001	11	48−79	advanced cancer	fatigue	prospective	10−30mg/day divided BID	9 (82%) improved, 89% of responses within 3d; also noted improvements in sedation, anorexia, and pain	AE in 6 (55%): severe agitation, insomnia and dry mouth leading to discontinuation in 1; mild AE: insomnia (4), nausea, anorexia
Sugawara, 2002	16	48−76	advanced cancer	fatigue	prospective	5−30mg/day	6 (38%) responded (fatigue rating 0 −100 improved >30%); mean change 23 points (p=0.01)	AE in 3 (19%), required discontinuation in 2: insomnia (2), palpitations
Bruera, 2003	31	24−79, median 51	advanced cancer	fatigue≥4/10	prospective	MP 5mg q2h prn fatigue (max 20mg/day)	fatigue improved a mean of 1.2 points from baseline to day 7 (p<0.001); also significant improvement in other symptoms and on a formal fatigue scale	AE in 7 (23%), required discontinuation in 0: restlessness (2), dizziness, anorexia (2), vertigo, tachycardia
Gagnon, 2004	14	41−80	advanced cancer	hypoactive delirium	prospective	10mg BID, titrated to response or AE	significant improvement in MMSE after 1st dose and on a stable dose; all reported improved energy	nervousness at high doses (>50 mg/d)

Author, Year	N	Age	Population	Diagnoses	Design	Treatments	Results	Adverse Effects
							and psychomotor retardation	
Hanna, 2006	37	35−69, median 51	breast cancer patients, cancer free for 6 months to 5 years	fatigue score above cutoff, minimal or no depression	prospective	MP 5mg BID, increased to 10mg at week 2 if fatigue score still high and no toxicity	20 (54%) improved (based on scores) at both 4 and 6 weeks	AE (all Grade 1): restlessness/ anxiety (6), dizziness (3), headache (3), palpitations, back spasm; discontinuation required in 6

MP: methylphenidate; BID: twice a day; TID: three times a day; AE: adverse effects; MMSE: Mini-Mental State Examination