Published in final edited form as:

Psychooncology. 2017 November ; 26(11): 1763–1769. doi:10.1002/pon.4220.

Randomized, Double-Blind, Placebo Controlled Study of Methylphenidate for the Treatment of Depression in SSRI-Treated Cancer Patients Receiving Palliative Care

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Abstract

Objective—To determine the effectiveness of methylphenidate for depression treatment in advanced cancer patients.

Methods—An 18-day randomized, double-blind, placebo-controlled clinical trial of methylphenidate for treatment of depression in selective serotonin reuptake inhibitor (SSRI)-treated patients with advanced cancer in hospice or receiving palliative care. The primary outcome was depression remission, defined as a 50% reduction in score on the Montgomery-Asberg Depression Rating Scale.

Results—Among 47 enrolled participants, 35 were randomized. At study day 18, 85% of the methylphenidate and 60% of the placebo group were in depression remission ($p = 0.22$). Mean time to depression remission was 10.3 days [standard error (SE) 1.8] in the methylphenidate and 8.1 (SE 1.3) in the placebo group ($p = 0.48$). The mean baseline score for the Hospital Anxiety and Depression Scale (HADS) was 10.4 in each group and decreased by 3.6 (SE 1.1) in the methylphenidate and 2.3 (SE 1.2) in the placebo group ($p = 0.51$) by day 18. Once in remission, 1 methylphenidate and 5 placebo participants relapsed to depression ($p=0.18$). There was no

difference in mortality between the groups during the trial. Trial results were limited by small sample size attributed to difficulties in recruiting terminally ill patients.

Conclusions—This trial failed to demonstrate that methylphenidate treatment in SSRI-treated patients had a significant effect on depression remission in advanced cancer patients. This study underscores the difficulties in conducting trials for symptom management in patients with shortened life expectancy.

Background

Major depressive disorder (MDD) can be diagnosed in up to 26% of advanced cancer patients [1–3]. MDD is associated with shortened survival, suicidality and increased pain symptoms [4]. Treatment of depression in this patient population is complicated by shortened life expectancy [1, 5]. Conventional antidepressant medications, such as tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRI), have a delayed onset of action of up to 8 weeks after initiation [6–8]. Therefore, many advanced cancer patients, especially those enrolled in hospice, do not live long enough to benefit from these typical medications.

The potential benefits of methylphenidate in this population are diminished depressive symptoms and initial efficacy within two to three days of treatment [9, 10]. Adverse effects requiring discontinuation of treatment are reported in less than 10% of patients [11, 12] and promptly resolve with discontinuation of treatment [13, 14]. Psychostimulants may also decrease opioid sedation [15] and improve cognitive function in patients with cancer [16]. Among two small clinical trials of methylphenidate for treatment of depression in patients with advanced cancer, one showed benefit even though only 44% of participants completed the study [12]; another showed a positive trend [17].

We conducted a randomized, double-blind, placebo-controlled clinical trial of methylphenidate for depression treatment in SSRI-treated patients with advanced cancer who were enrolled in hospice or receiving palliative care. The goals of this study were to: (i) compare methylphenidate to placebo in the context of ongoing SSRI use for treatment of depression in cancer patients and (ii) determine the adverse effects of methylphenidate in combination with SSRIs.

NLM Identifier NCT00129467

Methods

Patient Eligibility Criteria

Adults who were eligible for this trial had advanced cancer (solid tumor or blood), a diagnosis of major depressive disorder as determined by Structured Clinical Interview for Diagnosis (SCID) [18] and score on the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS) >19 [19], indicating significant depressive cognitive symptomatology, at study entry. The study was originally designed to recruit Veterans enrolled in one of four home hospices who care for Veterans and an eight bed Veterans Affairs (VA) hospice inpatient unit. Because of low recruitment, enrollment was expanded to

include outpatients at Oregon Health & Science University (OHSU) and the VA Portland Health Care System (VAPORHCS) with advanced cancer, whose goals of care were primarily palliative. Potentially eligible patients were referred by their oncologist, hospice nurse or primary care provider after screening with a single item depression scale.

Patients were excluded from study participation if they were cognitively impaired as determined by a score on the Short Portable Mental Status Questionnaire (SPMSQ) [20, 21] that was <7 or if they had a diagnosis of delirium as determined by the Confusion Assessment Method (CAM) [22, 23]. Patients with a history of, or current mental disorder in which depressive symptoms occur, but for which psychostimulants are contraindicated (e.g., psychotic disorder, other active severe substance abuse or history of stimulant abuse) were also excluded. Other notable exclusion criteria included: severe insomnia; treatment for depression with a non-SSRI antidepressant; other contraindications to methylphenidate or an SSRI such as history of significant cardiac disease, hypertension, advanced liver or renal disease; symptom score >4 on the Brief Psychiatric Rating Scale (BPRS) [24] of anxiety, elated mood, suspiciousness, hallucinations, excitement, distractibility or motor hyperactivity; severe anxiety defined as a score >11 on the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS) [25]; and patients with active suicidal ideation.

Random Assignment

Each participant was randomly assigned to receive either methylphenidate plus an SSRI or placebo plus SSRI with equal allocation to these two groups. For patients not on an SSRI at the time of enrollment, the SSRI was started on the same day as the methylphenidate. An adaptive randomization method was used [26]. This allowed treatment assignment probability to change depending on existing imbalance in stratification tables. Randomization was initially stratified according to type of setting (inpatient vs. outpatient) and SSRI use within one month prior to study enrollment. Due to slow recruitment, non-hospice palliative care patients were enrolled later in the course of the study and hospice versus non-hospice replaced type of setting in the stratification. Later, after finding an imbalance in patients receiving chemotherapy or radiation therapy, that may be life-prolonging, these treatments were added to the stratification.

Treatment Protocol

Blinded treatment began within 5 days of randomization. Participants received methylphenidate 5 mg (one capsule) twice daily for three days (days 1–3), then 10 mg (two capsules) twice daily for the remainder of the study (days 4–18). Participants assigned to placebo received one capsule of placebo twice daily for three days and then two capsules twice daily for the remainder of the study. Methylphenidate and placebo capsules were identical. If a participant had a 50% decrease in their depressive symptoms as measured by MADRS at the initial dose of methylphenidate or placebo, they were maintained at that lower dose as long as their MADRS score remained reduced by 50%. If a participant had adverse effects when increasing to twice daily, their dose was adjusted to one capsule twice daily.

All participants were treated with an SSRI. Participants who were taking an SSRI at the time of enrollment continued on the same medication during the 18-day blind treatment period. The prescribed dose was adjusted if it was more than the highest dose in the recommended range (i.e., fluoxetine to 40 mg, paroxetine to 40 mg, citalopram to 40 mg, and sertraline to 150 mg). Patients who were not on an SSRI at the time of enrollment were prescribed citalopram 10 mg per day for two weeks and then increased to 20 mg per day thereafter. Citalopram was started on day one of the study concurrently with the methylphenidate or placebo. A participant's SSRI was discontinued or decreased if the participant experienced moderate to severe side effects likely attributable to an SSRI.

Home visits were arranged for all study visits. Each participant was assessed by the study psychologist with a total of four post-baseline measurements over the 18 days of the study (days 3, 6, 12, and 18) following the first dose of methylphenidate or placebo. At baseline (day 0) and each post baseline visit participants were administered the MADRS, CAM, and selected BPRS items. The HADS was administered on days 0, 6, 12 and 18. On days 0, 3, 6, 12, and 18 blood pressure and pulse rate were checked to screen for study drug side effects. A standardized inquiry procedure was administered at each post baseline visit to ascertain adverse drug effects.

Outcome Measures

The primary endpoint was remission in depression at the end of 18-day treatment period, as determined by a 50% decrease in MADRS score. The MADRS was chosen as the primary depression measure because it minimizes physical symptoms of depression that may artificially inflate depression scores in patients with physical illness. Both the proportion of patients who had this remission and time to remission were compared between methylphenidate and placebo groups. Secondary endpoints included change in depression scales as measured by HADS and MADRS and overall survival between groups.

Analysis

The target sample size was 104 patients (52 per group), which would provide 80% power to detect 53% remission rate versus 20% remission rate between the methylphenidate and placebo groups, respectively. The sample size was based on a two sample t-test with 5% significance level and accounted for an expected 30% loss due to follow-up, deaths and withdrawals. Generalized Estimating Equations (GEE) method [27] was used to assess changes in MADRS depression scores over time in an intention-to-treat analysis. The GEE model offers flexible regression modeling for incomplete repeated measures data. The model included the main effects of treatment and time, as well as the treatment by time interaction effect. This allowed us to test for a linear trend in the MADRS scores over time. The linear trend was tested in each of the two groups, methylphenidate and placebo, separately.

Time to remission between the methylphenidate and placebo groups was estimated by the Kaplan-Meier method compared using a log-rank test. All participants were evaluated at the end of 18-day trial with respect to the presence or absence of depression. In this analysis, those who were alive, but did not go into remission were censored at day 18, and those who

died prior to the end of 18-day trial were censored at the time of their death. Wilcoxon rank sum test was used to compare HADS scores between groups.

All analyses accounted for stratification factors: treatment status, SSRI prescribed more than one month before study entry, life-prolonging treatment received and hospice enrollment. P values less than 0.05 were considered statistically significant. All analyses were generated using Statistical Analysis System (SAS) version 9.4.

Results

A total of 47 participants were enrolled; 12 participants were later excluded as they did not meet inclusion/exclusion criteria at study entry (e.g., MADRS score was not high enough, SPMSQ was too low, or stimulant abuse found on review of systems). Three additional participants were randomized, but did not start the study medication: two withdrew and one became ineligible secondary to worsening medical status (Figure 1). Among the total sample that received study drug, 78% were men, mean age was 64 years and the most common types of cancer were colon (38%) and lung (22%). The median number of days from first day of study drug (day 1) until death was 109 days (Intra-quartile range [IQR], 373 days) in the methylphenidate group and 118 days (IQR, 189 days) in the placebo group (Table 1).

Mean MADRS score at baseline was 26.8 (Standard Error [SE 1.1]) in the methylphenidate group and 25.0 (SE 0.5) in the placebo group. On day 18, 85% (11/13) of the methylphenidate group were in depression remission compared to 60% (9/15) in the placebo group ($p = 0.22$, Chi-square test), as determined by a 50% reduction in MADRS score from baseline. Response in the placebo group was high. For example, by day six of the study 69% of the placebo no longer met depression criteria. At day 18, mean MADRS score was 14.2 (SE 2.3) in the methylphenidate group and 16.6 in the placebo group (SE 1.8) (Table 2 & Figure 2). Using GEE analysis, the overall test for linear trend in the MADRS scores combining the two groups revealed a significant decreasing linear trend ($p < 0.001$). When restricting the analysis to the MADRS scores in the methylphenidate group, the linear trend test revealed a significant decreasing trend (estimated mean = -1.58 ; $p < 0.001$) which was larger than the observed decreasing trend in the placebo group (estimated mean = -1.05 ; $p < 0.001$). There was no significant difference when comparing these trends between groups ($p = 0.34$). The mean time to remission of depression was 10.3 days (SE 1.8) in the methylphenidate group and 8.1 days (SE 1.3) in the placebo group ($p = 0.48$, log-rank test). The mean HADS depression scale score for each group was 10.4 at baseline, but by day 18 had declined to 6.8 (SE 1.1) in the methylphenidate group and 8.1 (SE 1.2) in the placebo group ($p = 0.51$, Wilcoxon rank sum test) (Table 2). After first remission, 1 participant in the methylphenidate group (7%) and 5 participants in the placebo group (29%) experienced a relapse of their depression during the study ($p = 0.18$, Fisher's exact).

Ten participants did not complete the trial, including six from the methylphenidate group and four from the placebo group. Reasons for withdrawal from the methylphenidate group included death ($N = 1$), elevated blood pressure ($N = 1$), delirium ($N = 2$), nausea ($N = 1$), and patient decision to stop the trial unrelated to adverse effects ($N = 1$). Among the placebo treated patients withdrawal occurred because of death ($N = 1$), elevated blood pressure ($N =$

1), dizziness (N = 1) and intolerance of citalopram (N = 1). (Supplemental Table 1) There was no difference in mortality between groups during the 18-day trial period. At final data analysis, completed 12 months after the conclusion of the trial, 80% of the methylphenidate group and 88% of the placebo group were deceased.

Conclusions

In this trial we failed to show that among SSRI-treated patients with advanced cancer, who were enrolled in hospice or receiving palliative care, methylphenidate has a significant effect on depression remission compared to placebo. Patients in the methylphenidate group did, however, appear less likely to experience a relapse of their depression once in remission compared to patients in the placebo group, although not statistically significant. There was no mortality difference between groups during the trial. Trial results were limited by small sample size attributed to difficulties in recruiting patients from this very ill population. There was both an unexpectedly high response rate among subjects in the placebo group and considerable variability in depression scores over time, which impacted our ability to detect differences between groups. By day six of the study, 69% of the placebo group was in remission suggesting that an even larger sample size than the original analytic approach may not have been able to demonstrate a statistical difference. Our study underscores the difficulties in conducting randomized, controlled trials for symptom management in patients with shortened life expectancy.

Previous uncontrolled trials and case series of methylphenidate use in patients with severe illness have revealed good response rates for depression [28]. Unfortunately, randomized controlled trials of methylphenidate in patients with advanced cancer have had mixed results. Ng et al completed a four week, placebo-controlled trial of methylphenidate added to mirtazapine in 88 terminally ill patients with cancer, of whom 39 completed the study; methylphenidate was superior to placebo in treating depressive symptoms as measured by MADRS from day 14 [12]. Another study compared methylphenidate to placebo in 69 patients with advanced cancer and depressive symptoms (though not necessarily clinical depression). Methylphenidate showed a positive trend in the incidence of response that did not reach statistical significance [17]. Some randomized trials of treatment of fatigue with methylphenidate in patients with cancer included depression measures, although elevated thresholds for depressive severity were not required for inclusion. In two studies methylphenidate had no effect on depressive symptoms [29, 30]. In a third study of fatigue focused on hospice patients, methylphenidate had significant benefit on all depression measures among a subset of patients with clinically significant depression [11].

Our study did suggest a potential benefit of treatment with methylphenidate among depressed terminally ill cancer patients in reducing the depression relapse rate. Though not statistically significant, patients taking methylphenidate appear less likely to experience a relapse of their depression than patients in the placebo group within the 18-day study period. It is unclear if this represents a potential additional benefit of adjunctive methylphenidate use in these patients or if the variability in depression scores impacted the observed relapse rate differences between groups. A prospective study of mental disorders in Veterans enrolled in hospice at the VA Portland Health Care System found that patients have high

variability from day to day and week to week in their depression scores [31]. Another study in prostate cancer patients found similar depression variability [32]. In this patient population, the variability in depression scores should be considered in future trial designs.

We encountered a variety of barriers in conducting this trial and further discussion may prove valuable for future investigators attempting such research. Some barriers were foreseen, but attempts to mitigate the barriers had unanticipated effects. For example, among patients with shortened life expectancy, non-treatment of depression was deemed unethical and thought likely to negatively impact recruitment. Therefore, all participants received an SSRI. We reasoned that with both arms receiving some type of depression treatment study participation would increase, but also reasoned it was likely that over 18 days, any improvement attributable to SSRIs would be negligible. As such the SSRI was considered an “active placebo”. It is possible, however, that SSRI treatment contributed to the high placebo response. Even with a study design in which all patients received depression treatment, the study was closed for several months after continuing review by the OHSU Institutional Review Board when a new IRB Chair questioned whether it was ever ethical to enroll terminally ill patients into research studies. Shortened life expectancy also precluded the use of a “run-in” study design which could have assured depression persistence before starting treatment, potentially decreasing the placebo response. Another anticipated barrier in trial design was the added burden to hospice patients coming to the hospital for study visits. The social benefits of home visits from study psychologists, however, may have contributed to the high placebo response rate, undermining the trial’s ability to demonstrate a positive effect of methylphenidate. Despite these study accommodations, only half of the planned recruitment was achieved before project funds were expended.

Other barriers were unanticipated. For example, we experienced difficulty engaging oncologists in screening patients at the OHSU site. Some oncologists admitted they did not want to ask their patients if they were feeling sad or depressed because they were limited in accessing mental health referral for patients who did not enroll in the study. A second unanticipated barrier was secular changes in hospice enrollment from study planning to the beginning of recruitment wherein length of stay preceding death for patients with cancer at the largest participating hospice program declined from 17 to 12 days. Therefore, many hospice patients were too ill to be considered for enrollment and we expanded study eligibility to non-hospice patients. These barriers highlight the difficulties in conducting research in patients with shortened life expectancies.

The study has limitations. The most important was inadequate sample size which may have increased type II error. Utilization of SSRIs in both groups may have limited power to detect differences by contributing to the placebo response. Even though groups were stratified at randomization, imbalances in SSRI use at study entry or utilization of life-prolonging treatment between groups may have biased results in unpredictable ways.

In summary, among SSRI-treated patients we were unable to demonstrate that methylphenidate was superior to placebo in remitting depression among advanced cancer patients enrolled in hospice or receiving palliative care. Methylphenidate, however, may reduce depression relapse once in patients are in remission. Conducting symptom

management clinical trials in terminally ill patients is particularly challenging. Psychostimulants for depression treatment in patients with advanced cancer in hospice or palliative care deserve further study. Future studies may benefit from: cooperative designs such as multicenter trials or developing multidisciplinary partnerships to increase enrollment of terminally ill patients; sample size calculations that include a high placebo response rate; analytic methods that take into account day to day variability in depression scores among depressed patients with advanced cancer; methods to overcome referring providers concerns regarding depression screening; and IRB education regarding the ethics of trials in patients with terminal disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Sullivan is supported by an NIH-NCI grant 1K07CA190706-01A1. This material is based on work supported by the Department of Veterans Affairs, Veterans Health Administration, and Health Services Research and Development grant IIR03-194. This publication was made possible with support from the Oregon Clinical and Translational Research Institute (OCTRI) (UL1RR024140) from the NCRR, a component of the NIH. Biostatistics support was provided by the OHSU Knight Cancer Institute (NIH/NCI 5P30CA069533-16). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The Department of Veterans Affairs did not have a role in the conduct of the study, in the collection, management, analysis, interpretation of data, or in the preparation of the manuscript. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs or the U.S Government.

References

- Hotopf M, Chidgey J, Addington-Hall J, Ly KL. Depression in advanced disease: a systematic review Part 1. Prevalence and case finding. *Palliat Med.* 2002; 16:81–97. [PubMed: 11969152]
- Field, M., Cassel, K. Approaching death: improving care at the end of life. Institute of Medicine; Washington: 1997.
- Goy, E., Ganzini, L. Delirium, anxiety and depression. In: Morrison, R.Meier, D., Capello, C., editors. *Geriatric Palliative Care*. Oxford University Press; New York: 2003. p. 286-303.
- McDaniel JS, Musselman DL, Porter MR, Reed DA, Nemeroff CB. Depression in patients with cancer. Diagnosis, biology, and treatment. *Arch Gen Psychiatry.* 1995; 52:89–99. [PubMed: 7848055]
- Chochinov HM, Wilson KG, Enns M, Lander S. Prevalence of depression in the terminally ill: effects of diagnostic criteria and symptom threshold judgments. *Am J Psychiatry.* 1994; 151:537–40. [PubMed: 7511875]
- Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M. STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry.* 2006; 163:28–40. [PubMed: 16390886]
- Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. *Arch Gen Psychiatry.* 2006; 63:1217–23. [PubMed: 17088502]
- Nierenberg AA, Farabaugh AH, Alpert JE, Gordon J, Worthington JJ, Rosenbaum JF, Fava M. Timing of onset of antidepressant response with fluoxetine treatment. *Am J Psychiatry.* 2000; 157:1423–8. [PubMed: 10964858]
- Wallace AE, Kofoed LL, West AN. Double-blind, placebo-controlled trial of methylphenidate in older, depressed, medically ill patients. *Am J Psychiatry.* 1995; 152:929–31. [PubMed: 7755127]

10. Wagner GJ, Rabkin R. Effects of dextroamphetamine on depression and fatigue in men with HIV: a double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2000; 61:436–40. [PubMed: 10901342]
11. Kerr CW, Drake J, Milch RA, Brazeau DA, Skretny JA, Brazeau GA, Donnelly JP. Effects of methylphenidate on fatigue and depression: a randomized, double-blind, placebo-controlled trial. *J Pain Symptom Manage*. 2012; 43:68–77. [PubMed: 22208450]
12. Ng CG, Boks MP, Roes KC, Zainal NZ, Sulaiman AH, Tan SB, de Wit NJ. Rapid response to methylphenidate as an add-on therapy to mirtazapine in the treatment of major depressive disorder in terminally ill cancer patients: a four-week, randomized, double-blinded, placebo-controlled study. *Eur Neuropsychopharmacol*. 2014; 24:491–8. [PubMed: 24503279]
13. Masand PS, Tesar GE. Use of stimulants in the medically ill. *Psychiatr Clin North Am*. 1996; 19:515–47. [PubMed: 8856815]
14. Emptage RE, Semla TP. Depression in the medically ill elderly: a focus on methylphenidate. *Ann Pharmacother*. 1996; 30:151–7. [PubMed: 8835049]
15. Stiefel F, Die Trill M, Berney A, Olarte JM, Razavi A. Depression in palliative care: a pragmatic report from the Expert Working Group of the European Association for Palliative Care. *Support Care Cancer*. 2001; 9:477–88. [PubMed: 11680829]
16. Rozans M, Dreisbach A, Lertora JJ, Kahn MJ. Palliative uses of methylphenidate in patients with cancer: a review. *J Clin Oncol*. 2002; 20:335–9. [PubMed: 11773187]
17. Centeno C, Sanz A, Cuervo MA, Ramos D, Hernansanz S, Gonzalez J, Almaraz MJ, Lama M, Vara F, Nabal M, Pascual A. Multicentre, double-blind, randomised placebo-controlled clinical trial on the efficacy of methylphenidate on depressive symptoms in advanced cancer patients. *BMJ Support Palliat Care*. 2012; 2:328–33.
18. First, M., Spitzer, R., Gibbon, M., Williams, J. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P). Biometrics Research, New York State Psychiatric Institute; New York: 2002.
19. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979; 134:382–9. [PubMed: 444788]
20. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc*. 1975; 23:433–41. [PubMed: 1159263]
21. Smyer MA, Hofland BF, Jonas EA. Validity study of the short portable mental status questionnaire for the elderly. *J Am Geriatr Soc*. 1979; 27:263–9. [PubMed: 447988]
22. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990; 113:941–8. [PubMed: 2240918]
23. Pompei P, Foreman M, Cassel CK, Alessi C, Cox D. Detecting delirium among hospitalized older patients. *Arch Intern Med*. 1995; 155:301–7. [PubMed: 7832602]
24. Overall J, Gorham D. THE BRIEF PSYCHIATRIC RATING SCALE. *Psychological Reports*. 1962; 10:799–812.
25. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J Psychosom Res*. 1997; 42:17–41. [PubMed: 9055211]
26. Rosenberger, W., Lachin, J. Randomization in Clinical Trials: Theory and Practice. John Wiley & Sons; New York, NY: 2002.
27. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986; 42:121–30. [PubMed: 3719049]
28. Hardy SE. Methylphenidate for the treatment of depressive symptoms, including fatigue and apathy, in medically ill older adults and terminally ill adults. *Am J Geriatr Pharmacother*. 2009; 7:34–59. [PubMed: 19281939]
29. Butler JM Jr, Case LD, Atkins J, Frizzell B, Sanders G, Griffin P, Lesser G, McMullen K, McQuellon R, Naughton M, Rapp S, Stieber V, Shaw EG. A phase III, double-blind, placebo-controlled prospective randomized clinical trial of d-threo-methylphenidate HCl in brain tumor patients receiving radiation therapy. *Int J Radiat Oncol Biol Phys*. 2007; 69:1496–501. [PubMed: 17869448]

30. Bruera E, Valero V, Driver L, Shen L, Willey J, Zhang T, Palmer JL. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. *J Clin Oncol.* 2006; 24:2073–8. [PubMed: 16648508]
31. Goy ER, Ganzini L. Prevalence and natural history of neuropsychiatric syndromes in veteran hospice patients. *J Pain Symptom Manage.* 2011; 41:394–401. [PubMed: 20869843]
32. Sharpley CF, Christie DR, Bitsika V. Variability in anxiety and depression over time following diagnosis in patients with prostate cancer. *J Psychosoc Oncol.* 2010; 28:644–65. [PubMed: 21058161]

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Figure 1.

Figure 2. Depression Remission in the Methylphenidate and Placebo Groups

Percentage of participants in the methylphenidate and placebo groups with 50% reduction in MADRS score from baseline (remission) versus <50% reduction in MADRS score from baseline (depressed) during the 18-day trial (p=0.22).

Table 1

Baseline Characteristics

	Methylphenidate Group n=15	Placebo Group n=17
Characteristic	n (%)	
Gender, male	8 (53)	17 (100)
Age, mean (SD)	62 (15)	66 (13)
Race		
White	14 (94)	17 (100)
Black	1 (6)	0
Marital Status		
Married/partnered	4 (27)	8 (47)
Single	2 (13)	1 (6)
Divorced, Widowed	9 (60)	8 (57)
Years of Education, mean (SD)	13.5 (2.0)	11.9 (3.3)
Cancer Type		
Gastrointestinal	5 (33)	7 (41)
Pulmonary	2 (13)	5 (29)
Head and Neck	3 (20)	1 (6)
Other	5 (33)	4 (24)
ECOG Performance Status		
0-1	6 (40)	6 (35)
>1	9 (60)	11 (65)
SSRI use within one month study enrollment	6 (40)	8 (47)
Setting, Outpatient	7 (78)	11 (79)
Receiving Life-prolonging Treatment	4 (27)	8 (47)
End-of-life Care		
Hospice enrollment	5 (33)	7 (41)
Receiving palliative care	10 (67)	10 (59)
Enrollment Until Death, median days (IQR)	109 (373)	118 (189)

Abbreviations: SD= standard deviation, ECOG= Eastern Cooperative Oncology Group, SSRI= Selective Serotonin Reuptake Inhibitor, IQR= Intra-quartile range.

Table 2

MADRS and HADS Scores in the Methylphenidate and Placebo Groups

	Methylphenidate Group N= 15	Placebo Group N= 17
Characteristic	Mean (SE)	Mean (SE)
MADRS Score		
At baseline	26.8 (1.1)	25.0 (0.5)
At Day 18	14.2 (2.3)	16.6 (1.8)
HADS Score		
At baseline	10.4 (1.0)	10.4 (0.8)
At Day 18	6.8 (1.1)	8.1 (1.2)

Abbreviations: SD= standard deviation, MADRS= Montgomery-Asberg Depression Rating Scale, HADS= Hospital Anxiety and Depression Scale.

All p values for group comparisons >0.05