

CLINICAL INVESTIGATION

Brain

A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED PROSPECTIVE
RANDOMIZED CLINICAL TRIAL OF d-THREO-METHYLPHENIDATE HCL IN
BRAIN TUMOR PATIENTS RECEIVING RADIATION THERAPY

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Purpose: The quality of life (QOL) and neurocognitive function of patients with brain tumors are negatively affected by the symptoms of their disease and brain radiation therapy (RT). We assessed the effect of prophylactic d-threo-methylphenidate HCl (d-MPH), a central nervous system (CNS) stimulant on QOL and cognitive function in patients undergoing RT.

Methods and Materials: Sixty-eight patients with primary or metastatic brain tumors were randomly assigned to receive d-MPH or placebo. The starting dose of d-MPH was 5 mg twice daily (b.i.d.) and was escalated by 5 mg b.i.d. to a maximum of 15 mg b.i.d. The placebo was administered as one pill b.i.d. escalating three pills b.i.d. The primary outcome was fatigue. Patients were assessed at baseline, the end of radiation therapy, and 4, 8, and 12 weeks after brain RT using the Functional Assessment of Cancer Therapy with brain and fatigue (FACIT-F) subscales, as well as the Center for Epidemiologic Studies Scale and Mini-Mental Status Exam.

Results: The Mean Fatigue Subscale Score at baseline was 34.7 for the d-MPH arm and 33.3 for the placebo arm ($p = 0.61$). At 8 weeks after the completion of brain RT, there was no difference in fatigue between patient groups. The adjusted least squares estimate of the Mean Fatigue Subscale Score was 33.7 for the d-MPH and 35.6 for the placebo arm ($p = 0.64$). Secondary outcomes were not different between the two treatment arms.

Conclusions: Prophylactic use of d-MPH in brain tumor patients undergoing RT did not result in an improvement in QOL. © 2007 Elsevier Inc.

Fatigue, Quality of life, Cognitive function, Radiation therapy, Methylphenidate.

INTRODUCTION

Each year in the United States, approximately 17,500 primary brain tumors and more than 150,000 brain metastases are diagnosed. Taken together, primary and metastatic brain cancer is more common than newly diagnosed lung, breast, prostate, or colorectal cancer (1). The majority of patients with primary or metastatic brain tumors will have significant symptoms of their disease and brain radiation therapy that will negatively impact their quality of life (QOL) and neurocognitive function.

The impact of primary and metastatic brain tumors on QOL and neurocognitive function can be generally divided into three categories: global effects, left hemisphere effects, and right hemisphere effects. Global effects of brain tumors include drowsiness, fatigue, anxiety, depression, decreased motivation, apathy, and decreased short-term memory (2–5).

The acute side effects of radiation are defined as those occurring during and up to 3 months following treatment (6). The acute toxicity of whole brain radiation therapy (RT) has been reviewed by Kiebert *et al.* (7) and Scheibel *et al.* (4),

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and includes fatigue, malaise, decreased physical functioning, and overall well-being, as well as decreases in concentration, short-term memory, and visuomotor speed. Eardley (8) reviewed acute side effects in 39 patients with head and neck cancer receiving RT, the treatment fields of which typically encompassed the lower quarter to third of the brain to cover adequately the lymph nodes in the upper cervical regions and skull base. Symptoms were assessed at baseline, at the end of RT, and 7 weeks after completing RT. The most common side effects were fatigue, reported in two thirds of patients, and depression, seen in 47%. During the interval between the end of radiation and 7 weeks later, 53% of patients reported that their side effects were worse, 70% reported that side effects were still noticeable, and 70% were not back to baseline activity mostly because of persistent fatigue. At 7 weeks, 40% of patients still had significant side effects (8). Given the significance of these brain-RT-related side effects, attempts to improve QOL with medical therapy have been undertaken.

Methylphenidate is a mild CNS stimulant approved for use in patients with attention-deficit disorders and narcolepsy. It is rapidly absorbed from the upper small bowel and rapidly penetrates the blood-brain barrier (9, 10). Methylphenidate causes release of dopamine and norepinephrine from reserpine-sensitive, bound, stored, central catecholamine pools. In clinical trials, methylphenidate has been shown to enhance the rate of functional recovery in patients with closed head injuries, as well as to reduce the negative neuropsychological symptoms and improve cognition in patients with Alzheimer's and vascular dementias (11–13).

Clinical data on the use of methylphenidate in an attempt to improve QOL and neurocognitive function in patients with primary brain tumors and brain metastases is limited. The first report by Weitzner and colleagues (14) described three patients who had neurocognitive dysfunction related to arousal and psychomotor speed stemming from primary and metastatic brain tumors, RT, or both who benefited significantly from methylphenidate. Patients were initially given 5 mg twice daily (b.i.d.) with titration to 10 mg b.i.d. after 3 days. Improvements were noted in attention and mood, psychomotor speed, and visuomotor scanning speed. In addition, Meyers *et al.* (15) assessed the effect of methylphenidate on cognition and functional independence in 30 patients with malignant gliomas who received RT to the brain. Ability to function in activities of daily living and neurocognitive function were documented before and during treatment with methylphenidate. Patients received 10, 20, or 30 mg of methylphenidate b.i.d. on an inpatient dose escalation. Improvement in energy, motivation, stamina, mood, attention and concentration, visuomotor speed, verbal memory, expressive speech, and executive function were noted in the vast majority of patients. Adverse events (AEs) were noted in only two patients, both of whom were on the 20-mg twice-daily doses. These symptoms resolved immediately upon discontinuation of methylphenidate. There was no increase in seizure frequency, and the majority of patients on steroid therapy were able to decrease their dose.

d,l-methylphenidate (Ritalin), is the most widely prescribed drug for the treatment of attention-deficit/hyper-

activity disorder (ADHD). The clinical effectiveness of d,l-methylphenidate appears to reside in the d-isomer. In 1998, Celgene Corporation began a series of clinical trials to assess the efficacy and toxicity of d-MPH for ADHD. d-MPH provided a similar magnitude of benefit (90% efficacy) as d,l-methylphenidate in treating ADHD with similar to less toxicity. The most frequently reported d-MPH associated AEs were headache (24%), abdominal pain (14%), anorexia (14%), insomnia (8%), nausea (7%), nervousness (6%), emotional lability (4%), and motor tics (0.5%). Overall, d-MPH was well tolerated by patients. The AEs were consistent with the known and acceptable AEs for d,l-methylphenidate. The AE profile was unchanged with long-term treatment (up to 1 year), and no withdrawal symptoms were demonstrated.

Despite the availability of this information, stimulants are not widely used in irradiated brain tumor patients today. A lack of knowledge about the use of CNS stimulants in this setting and lack of appreciation for how one's QOL is affected by brain RT for primary and metastatic brain tumors may explain the reasons behind their underuse. As such, we designed a Phase III prospective randomized clinical trial in patients undergoing brain RT to provide information about the efficacy and toxicity of d-MPH in a controlled setting in which quality of life and neurocognitive function would be carefully measured.

PATIENTS AND METHODS

Eligibility and exclusion criteria

Signed protocol-specific informed consent and authorization before registration were obtained. Inclusion criteria were as follows: aged ≥ 18 years, metastatic brain tumor (histologic confirmation of primary or metastatic cancer), or histologically confirmed primary brain tumor (glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic mixed oligoastrocytoma, low-grade glioma, meningioma, or ependymoma); Karnofsky Performance Scale (KPS) ≥ 70 ; life expectancy ≥ 3 months; hemoglobin ≥ 10.0 , white blood cell count $\geq 1,500$, and platelets $\geq 75,000$; and planned brain RT (partial or whole brain) ≥ 2500 cGy.

Patients may have had previous chemotherapy and/or irradiation to sites other than the brain and were allowed to receive chemotherapy concomitantly with the brain irradiation.

Exclusion criteria included serious medical or psychiatric illness that would prevent informed consent, completion of protocol therapy, or completion of QOL questionnaires; history of hypersensitivity to d,l-methylphenidate or d-MPH (Ritalin or generic equivalent); patients with a history of steroid psychosis; patients with a history of or who were currently taking medications for attention-deficit disorder, anxiety disorder, schizophrenia, or substance abuse; patients taking antidepressants for any reason; patients with a family history of or active Tourette's syndrome; patients with history of or active glaucoma; patients who have received prior brain RT, including stereotactic radiosurgery; patients undergoing craniospinal axis irradiation; patients with hypertension or other cardiovascular disease requiring antihypertensives or other cardiovascular medications; and patients who are pregnant or breast-feeding.

Study instruments

The general Functional Assessment of Cancer Therapy (FACT) was developed to provide information about health-related QOL that is specific to cancer patients (16). The FACT consists of

27 questions with four domains assessing physical well-being (seven items), social/family well-being (seven items), emotional well-being (six items), and functional well-being (seven items). The validated Brain Subscale (FACT-Brain) adds 19 items to the general FACT that are specific to brain tumor patients (17), and the 13-item validated Fatigue Subscale (FACIT-F) addresses the physical and functional consequences of fatigue (18). Higher scores represent better QOL for each of these scales.

In this clinical trial, QOL was measured by a number of validated instruments. The addition of the Center for Epidemiologic Studies Depression Scale (CESD) (19) complements the FACT-Brain and the FACIT-F for the assessment of depression and mood. Global cognitive function was measured with the Folstein Mini-Mental State Exam (MMSE) (20). Higher scores represent a greater degree of depression for the CESD, whereas higher scores on the MMSE represent a higher degree of cognitive functioning.

Treatment

Participants included 68 patients with primary ($n = 33$) or metastatic ($n = 35$) brain tumors undergoing whole or partial brain RT who were entered into this randomized double-blind placebo-controlled study (Fig. 1). Patients underwent a planned course of fractionated external beam brain RT (partial or whole brain) with a total dose of ≥ 25 Gy in ≥ 10 fractions of 180–300 cGy each. After randomization, patients received a bottle of pills containing either the study drug (d-MPH 5-mg tablets) or a matched placebo. Patients had to begin the study drug by day 5 of radiation treatment. The first dose was to be taken before breakfast, the second dose before 6 PM. After 5–7 days, the dose was increased to two pills b.i.d., and after 10–14 days to 3 pills b.i.d. If the patient experienced any severe adverse events possibly, probably or definitely related to the study drug using the Common Toxicity Criteria Version 2.0, the dose was reduced by 1–2 pills/day to a minimum dose of 5 mg d-MPH (or one placebo pill) b.i.d. If this was not tolerated, all study medication was discontinued permanently. Patients were evaluated weekly during the radiation therapy to adjust the dose and assess the toxicity. Four weeks after the end of radiation therapy, patients were also reevaluated. The study drug was given during the duration of the brain RT and for 8 weeks after completion of the radiation. Patients were then tapered off of the study drug by reducing the dose by one pill b.i.d. every week. Patients underwent a final evaluation at 12 weeks after the completion of radiation.

A research nurse presented the study questionnaires to patients to complete the FACT, FACIT-F, FACT-Brain, and CESD and administered the MMSE in conjunction at the time of each visit. Patient-reported QOL and global cognitive function were at the following times: baseline, end of RT, and at 4, 8, and 12 weeks post-RT. Baseline and weekly prothrombin time/international normalized ratio (PT/INR) and anticonvulsant levels were also obtained before and during brain RT. Toxicities were recorded on a flow sheet as part of the physician assessment at each of the designated time points.

Statistical analysis

This randomized double-blind placebo-controlled trial was designed to compare the effects of d-MPH versus placebo on QOL and global cognitive function in patients with metastatic or primary brain tumors receiving external beam brain RT. Patients were stratified by tumor type (primary vs. metastatic), treatment (RT alone vs. RT + chemotherapy), and KPS (< 90 vs. ≥ 90) and randomized within strata to one of the two treatment arms with equal probability. The primary test for treatment efficacy was the comparison between 8 week post-RT mean fatigue level for those patients receiving

Stratify:

Primary vs Metastatic

Brain Tumor

1. Primary brain tumor
2. Metastatic brain tumor

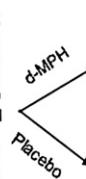
Treatment

1. RT Alone
2. RT + Chemo

Baseline KPS

1. 90 or 100
2. 70 or 80

R
A
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E



d-MPH 5 mg BID with dose escalations of 5 mg BID q 5-7 days up to 15 mg BID during RT. Continue drug at maximally tolerated dose \times 8 weeks after RT. Follow for 4 more weeks.

Placebo 1 pill BID with escalation of 1 pill BID q 5-7 days up to 3 pills BID during RT. Continue drug at maximally tolerated dose \times 8 weeks after RT. Follow for 4 more weeks.

Fig. 1. Trial schema. BID = twice daily dose; d-MPH = d-threo-methylphenidate HCl; KPS = Karnofsky Performance Scale; RT = radiation therapy.

d-MPH to that of patients receiving placebo. Eighty-one patients per group were needed to detect a 15% relative difference in the fatigue subscale of the FACIT-F (i.e., 36.8–42.3) with 90% power at the 5% two-sided level of significance. With this number of patients in each group, we would be also able to detect a 10% relative difference in QOL as quantitated by the FACT or FACIT-F with 90% power at the 5% two-sided level of significance. The primary outcome for this study, fatigue, was monitored according to a three-stage group sequential design that allowed early stopping for efficacy or futility. The first interim analysis was to be conducted after 54 patients, which, assuming that 20% would drop out, would require 68 actual accruals.

Two-sample t tests were used to assess the unadjusted differences between treatment groups in fatigue and other QOL measures at baseline and at each assessment time following randomization. Analysis of covariance was used to assess group differences in these outcomes at each assessment time after adjusting for pretreatment values, strata, age, and gender. All longitudinal data were analyzed using a mixed-model analysis of covariance to assess the treatment and time effects and their interaction. An autoregressive covariance structure was used to account for the within patient correlation over time. Because we had missing data (mostly due to patient dropout) and our analyses assume that these data are missing at random, we used t tests to assess differences in patient characteristics and outcome measures (before dropping out) between those who dropped out of and those who remained in the study. For example, baseline variables were compared between those who did and did not drop out before the end of RT measurements, whereas baseline and end of RT measurements were compared between those who did and did not drop out before 4 weeks post-RT.

RESULTS

Entered into the study were 68 patients, 34 in each treatment arm. The study accrued more slowly than expected and was closed prematurely because of withdrawal of support by the sponsoring drug company. Patient characteristics are summarized in Table 1 and are similar for the two groups. Patients ranged in age from 28 to 83 years, with medians of 52 and 60 for those receiving d-MPH and placebo, respectively ($p = 0.12$). Fifty-four percent of the patients were men, 84% were white, and 62% had a KPS of 100. Approximately half the patients had metastatic disease, and the majority (75%) were receiving RT without chemotherapy. Two patients dropped out of the study before receiving any therapy, 11 dropped out after their baseline assessment, 12 after the end of RT, and 11 after 4 weeks post-RT evaluation, leaving

Table 1. Patient characteristics

Characteristics	d-MPH		Placebo		<i>p</i> value
	<i>n</i> (%)		<i>n</i> (%)		
Total	34 (100)		34 (100)		
Age					0.12
Median (range)	52 (31–79)		60 (28–83)		
≥ 60 years	11 (32)		17 (50)		
Sex					0.47
Female	14 (41)		17 (50)		
Male	20 (59)		17 (50)		
Race					0.10
Black	7 (21)		3 (9)		
White	26 (76)		31 (91)		
Other	1 (3)		0 (0)		
Disease stage					0.81
Primary	16 (47)		17 (50)		
Metastatic	18 (53)		17 (50)		
Performance status					1.0
0	21 (62)		21 (62)		
1	13 (38)		13 (38)		
Treatment					0.78
RT + chemotherapy	9 (26)		8 (24)		
RT only	25 (74)		26 (76)		

Abbreviations: d-MPH = d-threo-methylphenidate HCl; RT = radiation therapy.

32 patients (47%) for the 8-week evaluation, a higher dropout rate than expected. Patients who dropped out of the study early did not differ significantly from those who remained in the study in fatigue, QOL, or cognition at any time before they dropped out. However, those who dropped out were significantly older and had significantly worse performance status than those who remained on study. Thus, it appears that early dropout is related to some of the patient covariates but not to the actual outcome measures. Age and performance status (as part of strata) are included in all the adjusted models presented subsequently.

Results for the primary outcome, fatigue, are summarized in Table 2. At baseline, the mean (\pm SE) FACIT-F fatigue subscale score was 34.7 ± 1.4 for the d-MPH patients and 33.3 ± 2.4 for the placebo patients ($p = 0.61$). The overall

Table 2. Raw means and standard errors for the Functional Assessment of Cancer Therapy Fatigue Subscale (FACIT-F) scores at baseline and least squares estimates posttreatment based on analysis of covariance adjusted for baseline values and other patient characteristics

Time	d-MPH			Placebo			<i>p</i> value*
	<i>n</i>	Mean	SE	<i>n</i>	Mean	SE	
1 (Baseline)	33	34.7	1.4	29	33.3	2.4	0.61
2–End RT	27	30.2	2.3	25	31.3	2.5	0.72
3–4 Weeks	20	28.2	2.9	21	30.5	2.9	0.54
4–8 Weeks	11	33.7	3.5	17	35.6	2.8	0.64
5–12 Weeks	9	34.5	4.0	9	36.0	4.0	0.79

Abbreviations: d-MPH = d-threo-methylphenidate HCl; RT = radiation therapy.

* *t* test at baseline, analysis of covariance elsewhere.

mean (\pm SD) of 34.0 ± 10.4 was similar to the 36.8 ± 10.5 anticipated during the design of the study. By 8 weeks post-RT, the least squares estimated means (\pm SEs) adjusted for patient characteristics, were 33.7 ± 2.3 for the d-MPH and 35.6 ± 2.5 for the placebo arm ($p = 0.64$). The estimated effect of d-MPH on the fatigue subscale score at 8 weeks post RT was -1.9 (95% confidence interval [CI], -9.6 – 5.8). A mixed model analysis of covariance was used to assess the treatment effect on fatigue over time. Time, treatment, and the time by treatment interaction were included in the model along with the covariates mentioned above. Least squares estimated means from this model are shown in Fig. 2. The interaction between time and treatment was nonsignificant ($p = 0.69$) and was removed from the model. Neither time ($p = 0.58$) nor treatment ($p = 0.26$) were significantly associated with fatigue. The average treatment effect across time was -2.13 (95% CI, -5.76 – 1.49). Age was significantly associated with fatigue ($p = 0.01$), with the mean fatigue score lower by 0.23 units for each additional year of age.

The secondary QOL outcomes are summarized in Table 3. None of these outcomes including overall QOL measured by the FACT, brain QOL measured by the subscale score, depression measured by the CESD, and global cognition assessed by the MMSE differed significantly by treatment arm at 8 weeks posttreatment or across the entire follow-up period.

Toxicity and noncompliance

Only four patients (6%) experienced toxicity in the study. Two patients reported nausea and vomiting, one patient reported tachycardia (this patient was on the placebo arm), and one patient went off study because of increased liver enzymes.

DISCUSSION

This study was undertaken with the hope of validating previous retrospective reports of methylphenidate-associated

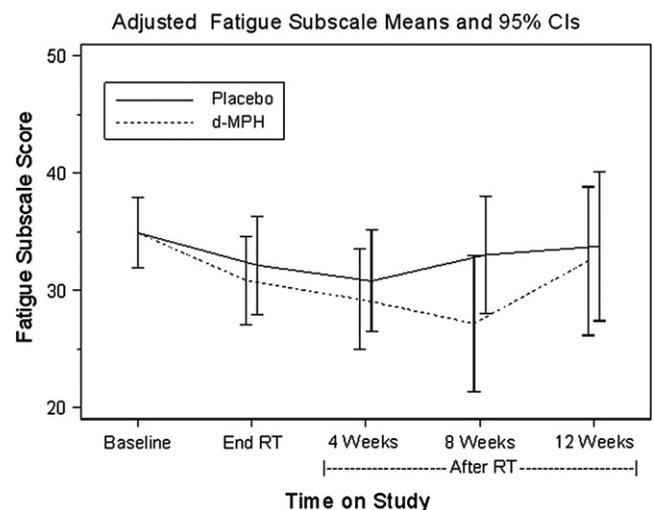


Fig. 2. Adjusted fatigue subscale means and 95% confidence intervals (CIs) based on longitudinal model. d-MPH = d-threo-methylphenidate HCl; RT = radiation therapy.

Table 3. Raw means and standard errors for the secondary quality of life outcomes at baseline and least squares estimates posttreatment based on analysis of covariance adjusted for baseline values and other patient characteristics

Outcome	Baseline			End radiation treatment			8 weeks		
	<i>n</i>	Mean	SE	<i>n</i>	Mean	SE	<i>n</i>	Mean	SE
FACT									
d-MPH	34	74.3	1.9	27	75.7	3.2	11	79.4	5.2
Placebo	29	78.1	2.7	25	79.8	3.6	17	78.0	3.9
FACIT-F									
d-MPH	33	108.9	3.0	27	105.7	4.9	11	114.2	7.3
Placebo	29	111.4	4.4	25	111.4	5.5	17	114.3	5.7
FACT-Br									
d-MPH	34	122.4	3.1	27	125.3	4.8	11	135.1	8.2
Placebo	29	128.1	4.7	24	129.8	5.3	15	130.4	6.2
Brain Subscale									
d-MPH	34	48.1	1.7	27	49.5	2.2	11	55.1	4.1
Placebo	29	50.0	2.4	24	50.0	2.4	15	52.2	3.2
CESD									
d-MPH	33	14.6	1.5	26	16.6	1.7	11	15.1	2.6
Placebo	29	14.6	1.6	24	14.6	1.8	16	16.4	2.0
MMSE									
d-MPH	34	27.2	0.5	29	26.4	1.1	15	23.3	2.7
Placebo	32	26.5	0.6	26	27.8	1.2	17	25.6	2.8

Abbreviations: CESD = Center for Epidemiologic Studies Depression Scale; d-MPH = d-threo-methylphenidate HCl; FACT = Functional Assessment of Cancer Therapy; FACT-BR = FACT Brain Subscale; FACIT-F = FACT Fatigue Subscale; MMSE = Mini-Mental State Exam.

improvements in cancer-related fatigue and QOL in brain tumor patients. Our study, a phase III randomized placebo-controlled double-blind trial, examined whether escalating doses of d-MPH in irradiated brain tumor patients, given prophylactically, would reduce fatigue and enhance QOL and cognitive function. Because of a slower than expected accrual, a higher than anticipated dropout rate, an interim analysis demonstrating no effect for d-MPH, and withdrawal of support by the sponsoring drug company, we elected to close the study.

Mulhern *et al.* (21) performed the first prospective study to examine the effects of two standardized doses of methylphenidate in children with acute lymphoblastic leukemia or malignant brain tumor status after post-multimodality treatment, and demonstrated statistically significant improvements in attention and cognition. The study did not escalate dose but was able to demonstrate outcome improvement.

In patients with non-CNS tumors, a recent abstract by Lower *et al.* (22) demonstrated that d-MPH was well-tolerated and significantly more effective than placebo in improvement of fatigue and impaired memory after chemotherapy in cancer patients. This study included adult patients (primary or metastatic brain tumors excluded) treated with ≥ 4 cycles of cytotoxic chemotherapy. Patients were randomized to an 8-week double-blind study. Dosing of d-MPH or placebo was adjusted from 10 to 50 mg/day, similar to our study, and maintained for ≥ 2 weeks. Endpoints included change from baseline in fatigue measured by FACIT-F and cognition measured by High Sensitivity Cognitive Screen (HSCS). Overall, 152 patients were randomized to placebo ($n = 75$) or d-MPH ($n = 77$). One hundred and thirty-two patients completed the study, with a significant ($p < 0.05$)

improvement in the FACIT-F Total Score and HSCS Memory Subscale observed in the d-MPH group versus placebo. The mean highest d-MPH dose was 27.7 mg/day, with common AEs being headache and nausea reported in 41% and 28% of patients receiving d-MPH, respectively. This study demonstrated that patients with non-CNS tumors derive a benefit in fatigue reduction and improved cognition from d-MPH.

Finally, a recently published preliminary report from Bruera *et al.* (23) in an open-label Phase II study demonstrated that patient-controlled methylphenidate administration rapidly improved fatigue and other symptoms. In this series of 31 patients, multiple symptoms were assessed daily with the FACIT-F, the primary endpoint being fatigue (23). This study did not include brain tumor patients (primary or metastatic) but demonstrated symptomatic improvement after the administration of methylphenidate in cancer patients.

In conclusion, our Phase III randomized trial did not demonstrate an advantage for prophylactic d-MPH on fatigue, QOL, or global cognition in patients with primary or metastatic brain tumors. Reasons for the negative results include lack of efficacy for d-MPH, small sample size, and a high dropout rate, reflecting the poor prognosis of the patient population. Although the study was stopped prematurely, these results indicate that d-MPH is unlikely to show a benefit in this patient population. For now, therapeutic rather than prophylactic methylphenidate is recommended for patients undergoing brain RT who develop fatigue or cognitive dysfunction. Given the prevalence of brain neoplasms, and the high incidence of these symptoms in brain-irradiated patients, further research in this area is warranted.

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