J Neurooncol
DOI 10.1007/s11060-011-0723-1

CLINICAL STUDY – PATIENT STUDY

# A randomized trial on the efficacy of methylphenidate and modafinil for improving cognitive functioning and symptoms in patients with a primary brain tumor

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Received: 15 July 2011 / Accepted: 17 September 2011


**Abstract** Limited research is available regarding the efficacy of psychostimulants in treating cognitive function in primary brain tumor patients. An open-label, randomized, pilot trial examined both the general and differential efficacy of 4 weeks of methylphenidate (MPH) and modafinil (MOD) in 24 brain tumor patients. Participants completed cognitive tests and self-report measures of fatigue, sleep disturbance, mood and quality of life at baseline and after 4 weeks.

Following stimulant treatment, there was evidence of a beneficial effect on test performance in speed of processing and executive function requiring divided attention. Patients with the greatest deficit in executive function at baseline appeared to derive the greatest benefit following stimulant therapy. Inconsistent, differential effects were found on a measure of attention in favor of MPH and on a measure of processing speed in favor of MOD. There was also evidence of a general beneficial effect on patient-reported measures of fatigue, mood, and quality of life, with no statistically significant differences between treatment arms in these measures over time. The results from this small pilot study should be interpreted with caution, but appear to warrant additional research, in larger study samples, targeting fatigue, processing speed and executive function, and exploring different doses of stimulants. Future studies may also wish to explore the specific patient factors that may be associated with responsiveness to psychostimulant treatment.

**Keywords** Cognitive deficit · Brain tumor · Psychostimulant · Stimulant treatment

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## Introduction

Impaired cognitive function including inattention and slowed information processing is common in patients with a primary brain tumor (PBT) and may be caused by the tumor itself and/or treatment [1]. There is limited empirical evidence supporting interventions to improve cognitive dysfunction in PBT patients. However, in recent years interest has grown resulting in studies of both cognitive rehabilitation approaches and pharmacological treatments [2].

With respect to the pharmacological treatment of cognitive deficits, psychostimulants, such as methylphenidate (MPH), have been most studied. MPH is a mild central nervous system stimulant, with pharmacologic properties similar to those of amphetamine. It increases synaptic

Published online: 02 October 2011

concentrations of dopamine and norepinephrine in the brain [3, 4], ultimately enhancing neural signal processing, predominantly within the prefrontal cortex [5]. Clinically relevant doses of MPH have been shown to improve cognitive processes in humans with and without attention deficit [5]. Besides MPH's traditional use in the treatment of attention deficit and narcolepsy, it has also been studied in Parkinson's disease [6], traumatic brain injury [7], medically ill older adults, and healthy individuals [8], based on its potential effects on cognitive function, depression and fatigue. However, a potential disadvantage of immediate release (IR) MPH is a relatively short half life requiring dosing two to three times a day. This practical limitation led to the development of sustained release (SR) MPH, which offers the convenience of once-daily dosing.

Modafinil (MOD) has also been developed and marketed as a novel wakefulness promoting drug. Originally, the mechanism of action of MOD was thought to differ from that of stimulant medications in that it was believed to have a nondopamine mechanism that would have more selective effects on cognitive function than MPH by specifically targeting aspects of attention and inhibitory control [9]; [10–12]. However, recent findings have provided evidence for the role of dopamine and norepinephrine in MOD's pharmacological actions [9, 13, 14]. MOD has traditionally been prescribed to treat narcolepsy and other sleep disorders. However, it has also been studied in populations with attention deficit, schizophrenia [14], multiple sclerosis [15] and cancer [16], and healthy and sleep-deprived individuals [8] to enhance cognitive functioning and ameliorate fatigue.

Limited research is available regarding the efficacy of these psychostimulants in treating impaired cognitive function among PBT patients. Three studies using either MPH or MOD reported positive effects on various cognitive domains, however they did not include a non-treatment control group to account for practice effects and nonspecific treatment effects [17–19]. The one double-blind randomized placebo-controlled study [20] that assessed the effect of prophylactic dexmethylphenidate in patients undergoing radiotherapy was closed prematurely owing to slow accrual and high drop-out. Underpowered analyses did not provide evidence of any positive effect on fatigue or cognitive functioning.

On the contrary, numerous studies have been conducted on the use of psychostimulants to reduce fatigue and depression among (non-brain) cancer patients, reporting modest successes [21, 22], and indicating acceptable safety and tolerance [23]. Furthermore, the efficacy of both MPH and MOD for improving cognitive function in this population has also received attention from researchers [24–30].

The objective of the current open-label, randomized pilot trial was to compare IR-MPH with SR-MPH and MOD for the improvement of cognitive function and symptoms in PBT patients. Based on the early assumptions about the more selective mechanisms of action of MOD, it was hypothesized that MOD would have greater effects than MPH on measures of attention. Furthermore, it was expected that patients receiving MPH, regardless of form (i.e., IR versus SR) would demonstrate greater improvement relative to MOD treated patients on tests of memory, psychomotor processing speed and selective tests of executive function, consistent with the findings in an earlier phase I study [18]. Both MPH and MOD were expected to produce similar improvement on measures of fatigue, sleep, mood and quality of life.

## Methods

### Participants

An open-label, randomized, pilot trial was designed to measure the differential efficacy of IR-MPH, SR-MPH, and MOD for the treatment of cognitive dysfunction and symptoms among PBT patients. This trial was approved by the institutional review board of the University of Texas M. D. Anderson Cancer Center (Houston, TX) and has been registered at www.clinicaltrials.gov as NCT00418691. PBT patients were considered eligible for participation if they subjectively complained of cognitive decline or fatigue, and were secondarily being considered for stimulant therapy by their neuro-oncologist. Additional inclusion criteria included (1) KPS $\geq$ 70, (2) age $\geq$ 18 and (3) the ability to speak and understand English or Spanish. Exclusion criteria included (1) current use of psychostimulants, monoamine oxidase inhibitors, anticoagulants, drugs similar to erythropoietin, or illicit drugs, (2) history of hypersensitivity reaction to MPH or MOD, (3) history of uncontrolled seizures, cardiac or pulmonary disease, (4) uncontrolled hypertension (systolic $>$ 140 mm Hg, diastolic $>$ 90 mm Hg, or not on a stable dose of anti-hypertensive medication for the past month), (5) severe headaches, (6) glaucoma, (7) narcolepsy, (8) Tourette's syndrome, (9) major psychiatric diagnosis, (10) alcohol or drug abuse, (11) current use of herbals/supplements for fatigue relief, e.g. gingko, ginseng, St. John's Wort, dehydroepiandrosterone, (12) unstable dose of antidepressants, and (13) other comorbidities or medications that in the treating physician's opinion could potentially interfere with safe administration of MPH or MOD.

Based on previous data [10, 18], a sample of 75 patients (25 per group) was determined to provide a power of 0.9, at the $P = 0.01$ significance level (and a standardized effect size of 1.13) to detect between arm differences in cognitive function.

## Procedure

After consenting to the study, patients were stratified by tumor location (i.e., right versus left hemisphere) and randomly assigned to one of three conditions:

1) 10 mg b.i.d. of methylphenidate IR (Ritalin; IR-MPH) for 4 weeks
2) 18 mg q.d. (AM) of methylphenidate SR (Concerta; SR-MPH) for 4 weeks
3) 200 mg q.d. (AM) of modafinil (Provigil; MOD) for 4 weeks.

Patients completed cognitive testing as well as self-report measures of fatigue, sleep disturbance, mood and quality of life at the time of registration (Day 0) and after treatment (median = Day 30; mean = 31.5, SD = 4.5 days). Toxicity was monitored at the follow-up visit and was defined as the most common MPH or MOD adverse effects that are intolerable to the patient including: nervousness, headache, dizziness, abdominal pain, fever, flu syndrome, insomnia, anorexia, and nausea.

## Measures

The cognitive test battery included widely-used standardized psychometric instruments that have published normative data based on age, education, handedness and gender (Table 1). Alternate test forms were used when possible to minimize practice effects. Patient-reported outcomes included measures of fatigue, sleep, depression, anxiety, sleep disturbance, and quality of life (Table 1).

## Statistical analyses

Due to slow accrual, only 34 of the 75 planned patients were enrolled in the study. Given the small sample size in the study, an exploratory approach to the analyses was employed. Both the MPH groups were aggregated into one group to allow comparison of the efficacy of MPH versus MOD in the final analyses. Baseline group differences in sociodemographic, clinical, cognitive test scores and symptom questionnaire variables were examined with independent *T* tests. We sought to determine if there was a beneficial general stimulant effect in the total study sample

**Table 1** Cognitive tests, mood, symptom and quality of life measures grouped by domain

| Domain | Measure | Abbreviation |
|---|---|---|
| Attention | WAIS-III Digit Span[a] | Dig-Span |
| Speed of Processing | WAIS-III Digit Symbol[a] | Dig-Sym |
| | Trail Making Test Part A | TMTA |
| Memory | HVLT-R Immediate Recall (Trials 1–3) | HVLT-R IR |
| | HVLT-R Delayed Recall | HVLT-R DR |
| | HVLT-R Delayed Recognition | HVLT-R DRecog |
| Executive Function | Trail Making Test Part B | TMTB |
| | MAE Controlled Oral Word Association[a] | COWA |
| Motor Dexterity | Lafayette Grooved Pegboard dominant hand | Peg-D |
| | Lafayette Grooved Pegboard non-dominant hand | Peg-ND |
| Functional Independence[b] | Functional Independence Measure | FIM |
| Fatigue | Brief Fatigue Inventory | BFI Total |
| | POMS Fatigue-Inertia | POMS-Fat |
| | POMS Vigor-Activity | POMS-Vig |
| Sleep | Brief Sleep Disturbance Scale | BSDS |
| Mood/Affective State | Beck Depression Inventory-II | BDI-II |
| | STAI State anxiety | STAI-State |
| | STAI Trait anxiety | STAI-Trait |
| | POMS Confusion-Bewilderment | POMS-Conf |
| | POMS Tension-Anxiety | POMS-Ten |
| | POMS Depression-Dejection | POMS-Dep |
| | POMS Anger-Hostility | POMS-Ang |
| Quality of Life | FACT-General score | FACT-G |
| | FACT-Brain module score | FACT-BR |
| | FACT-Total score | FACT-TOT |

*WAIS-III* Wechsler Adult Intelligence Scale-Third Edition, *HVLT-R* Hopkins Verbal Learning Test-Revised, *MAE* Multilingual Aphasia Examination, *POMS* Profile of Mood States, *STAI* State-Trait Anxiety Inventory, *FACT* Functional Anxiety of Cancer Therapy

[a] Use of standardized scores, in which calculation was based on published normative data for age, education, handedness and/or gender

[b] Only measured at baseline

and if there was a differential effect attributable to the specific stimulant agent. Two statistical approaches were employed to analyze group mean changes as well as the proportion of individuals who exhibited a clinically meaningful improvement. Given the small sample and exploratory nature of the analyses, no corrections for multiple statistical testing were applied and alpha level of $\leq 0.05$ was used to establish statistical significance. For all statistical tests, PASW Statistics 17.0 (SPSS Inc. Chicago, Illinois) was used.

*Analysis of stimulant effects on group means*

*T* tests comparing the mean scores from the follow-up assessment with the baseline assessment were performed to determine if there was evidence of a beneficial treatment effect.

*Analysis of individual improvement after stimulant treatment*

Meaningful improvement in outcome measures at the level of the individual patient was also determined. Change in cognitive tests scores relative to baseline was calculated and patients were categorized as improved, versus stable/declined using the practice effect adjusted reliable change index (RCI + PE) based on Chelune [31]. The RCI was derived from the standard error of measurement of each cognitive test using published normative data from healthy controls [32–35]. Based on a (pre-determined) 90% confidence interval, the difference in test score from baseline to the next assessment, that would be expected if no real change occurred, can be calculated as follows:

$$\mathrm{RCI} = 1.64(\mathrm{SE_{diff}}),\ \text{where}\ \mathrm{SE_{diff}} = [2(\mathrm{SEM})^2]^{1/2}$$
$$\text{and}\ \mathrm{SEM} = \mathrm{SD}_1(1 - \mathrm{r}_{12})^{1/2}$$

where SD is the standard deviation of the baseline assessment, SEM is the standard error of measurement, and r is the test–retest reliability statistic. All RCI thresholds were rounded to the nearest whole number. After adjusting for the mean practice effect, changes that did not meet the RCI threshold for improvement were categorized as non-improved (i.e., stable or declined) performance. Subsequently, the statistical significance of the proportion of patients with cognitive improvement was determined with a binomial test.

For each self-report measure, a minimally important difference (MID) criterion was calculated based on the standard approach used with health-related quality of life measures [36], which sets the MID criterion at 0.5 standard deviation (SD) from the mean of the total study group scores at baseline. This criterion was (liberally) applied to all symptom outcome measures used in this study. As binomial statistical testing was not possible for these measures, 90% confidence intervals for the proportion of improvers were calculated with the binomial formula.

*Comparative analysis of effects of MPH and MOD treatment on subgroup means*

Potential differential effects of treatment with either MPH or MOD on cognitive tests and self-report measures were analyzed with repeated measures analyses of covariance (RM-ANCOVA), always using the baseline test score or self-report rating as a covariate.

Other possible confounders were identified based on observed differences in sociodemographic or clinical variables between groups at baseline and the associations of these variables with the outcome measure. In order to obtain parsimonious models, given the small sample sizes, covariates were maintained in the RM-ANCOVA model if they had a statistically significant multivariate contribution. Otherwise, the analysis was conducted without that covariate.

*Comparative analysis of individual improvement after MPH and MOD treatment*

Differences in proportions of patients with improvement on cognitive tests and self-report measures in the MPH versus the MOD group were tested with Fisher's exact tests.

## Results

### Patient recruitment

This trial enrolled patients from March, 2004 until February, 2009 and was terminated due to slow accrual. Of the 34 patients accrued, 24 were randomized to MPH (11 were randomized to the IR-MPH group, 13 to the SR-MPH group) and 10 to the MOD group. Ten patients subsequently dropped out or were excluded from analysis. Patients were excluded due to tumor progression (MPH = 2, MOD = 1) and delirium associated with an infection requiring hospitalization (MOD = 1). Patients dropped out for the following reasons: prescription not filled (MPH = 2, MOD = 1), discontinued medication due to nausea (MOD = 1, possibly related to study medication) or hyperactivity (MOD = 1, believed to be related to increased steroid dose) and missed follow-up (MPH = 1).

### Baseline group comparisons

Despite randomization, the MOD group had a significantly higher proportion of male participants, and a higher mean

age than the MPH group (Table 2). For HVLT-R DRecog only, gender remained as a significant multivariate covariate in the model. There were no statistically significant differences in clinical variables, cognitive test scores or self-report measures between groups (Tables 2 and 4).

### Stimulant effects on group means

PBT patients demonstrated improvement in Dig-Sym and TMTB after stimulant treatment. Unexpectedly, cognitive performance declined after treatment in COWA and HVLT-R DRecog. Post-hoc *T* tests indicated that the change in these cognitive scores was not significantly related to radiographic evidence of progressive disease (PD) within 16 weeks after study completion ($P = 0.81$; $P = 0.07$, respectively), although there was a statistical trend for HVLT-R DRecog-score. It should be noted that there was no difference in the number of patients with post study PD within 16 weeks between the MPH and MOD groups (Table 2).

With regard to the symptom scores, improvement in symptoms after stimulant treatment was observed on nearly all of the measures (Table 3).

### Individual improvement after stimulant treatment

On the TMTB, 32% of patients evidenced improvement based on the RCI + PE after stimulant treatment, which was significant according to the binomial test. No other cognitive test demonstrated a statistically significant rate of improvement (Table 3). More than 50% of the total group reported symptom improvement based on the MID for the BDI-II, POMS-Fat, and POMS-Conf, with a mean magnitude of 0.5–0.7 SD.

### Effects of MPH and MOD treatment on subgroup means

Statistically significant differences in mean cognitive scores between groups over time (Table 4) were observed in both Dig-Span and TMTA. The patterns of results

**Table 2** Study sample characteristics

| | MPH ($N = 19$) | MOD ($N = 5$) | *P* |
|---|---|---|---|
| Age in years: mean (SD) | 42.5 (10.2) | 54.4 (7.7) | 0.02* |
| Education in years: mean (SD) | 14.8 (2.1) | 13.0 (3.0) | 0.12 |
| Follow-up period in days: median (Range) | 29.0 (28–44) | 30.0 (26–36) | 0.87 |
| Time since surgery in days: median (Range) | 370 (103–3334) | 1105 (315–4413) | 0.19 |
| FIM baseline score: mean (SD) | 120 (6.8) | 116 (9.9) | 0.32 |
| Gender (% Male) | 42% | 100% | 0.03* |
| Handedness (% Right) | 95% | 100% | 1.00 |
| Hemisphere of tumor (% Left) | 58% | 80% | 0.62 |
| Tumor type (% Glioma)[a] | 84% | 100% | 1.00 |
| Tumor grade (%) | | | 0.81 |
| Grade II | 16% | 0 | |
| Grade III | 37% | 40% | |
| Grade IV | 32% | 60% | |
| N.A. (No gliomas) | 16% | 0 | |
| History of surgery (%) | | | 0.64 |
| None | 5% | 0 | |
| Biopsy | 10% | 20% | |
| Resection | 85% | 80% | |
| History of radiotherapy (% Yes) | 79% | 100% | 0.54 |
| History of chemotherapy (% Yes) | 84% | 100% | 1.00 |
| Chemotherapy during study (% Yes) | 63% | 60% | 1.00 |
| PD $\leq$ 16 weeks after participation (% Yes) | 24%[b] | 20% | 1.00 |

*SD* Standard deviation, *PD* progressive disease

Differences in means were analyzed with independent *T* tests, differences in medians with Mann–Whitney (exact) tests, and proportions with Fisher's exact tests; * $P < .05$

[a] Other tumor types: medulloblastoma (1), primary CNS lymphoma (1), hemangiopericytoma (1)

[b] Data of two individuals missing (moved to other hospital)

**Table 3** General stimulant effects on cognitive tests and self-report symptom measures in total study sample: analyses of group means and frequency of improvement

| | | T1 | T2 | Sample size | *T* test | RCI + PE / MID improvement | Binomial testing/90%-confidence interval[3] | Mean change[a] |
|---|---|---|---|---|---|---|---|---|
| | Measure | Mean (SD) | Mean (SD) | *N* | *P* | % (*N*) | *P*/% | Z (SD) |
| Cognitive tests[1] | Dig-Span | −0.29 (1.17) | −0.38 (1.17) | 24 | 0.54 | 0 (0) | 1.00 | −0.10 (0.52) |
| | Dig-Sym | −0.86 (1.08) | −0.57 (1.32) | 24 | 0.02* | 8 (2) | 0.71 | 0.29 (0.56) |
| | TMTA | −1.67 (3.33) | −2.38 (6.30) | 23 | 0.38 | 4 (1) | 0.90 | −0.71 (3.80) |
| | TMTB | −2.95 (5.60) | −1.66 (4.16) | 22 | 0.02* | 32 (7) | <0.01* | 1.29 (2.24) |
| | HVLT-R IR | −1.57 (2.12) | −1.58 (2.21) | 23 | 0.80 | 4 (1) | 0.91 | −0.04 (1.02) |
| | HVLT-R DR | −1.81 (2.41) | −1.40 (2.40) | 23 | 0.05 | 0 (0) | 0.91 | 0.39 (0.98) |
| | HVLT-R DRecog | −0.53 (1.23) | −1.23 (1.75) | 23 | 0.03* | 4 (1) | 1.00 | −0.73 (1.54) |
| | COWA | −0.55 (1.19) | −0.88 (1.13) | 24 | 0.02* | 0 (0) | 1.00 | −0.33 (0.58) |
| | Peg-D | −3.99 (6.49) | −4.41 (8.27) | 24 | 0.53 | 8 (2) | 0.71 | −0.42 (3.56) |
| | Peg-ND | −2.68 (4.91) | −1.61 (2.61) | 22 | 0.68 | 14 (3) | 0.38 | 0.12 (1.98) |
| Symptom measures[2] | BFI Total[b] | 40.25 (21.60) | 32.33 (19.42) | 24 | 0.04* | 46 (11) | 29–63% | 0.37 (0.17) |
| | POMS-Fat[b] | 13.46 (6.50) | 9.04 (6.40) | 24 | <0.01* | 50 (12) | 33–67% | 0.68 (0.18) |
| | POMS-Vig | 13.38 (7.75) | 15.71 (7.09) | 24 | 0.04* | 46 (11) | 29–63% | 0.30 (0.14) |
| | BSDS Sleep[b] | 22.58 (11.36) | 20.29 (9.25) | 24 | 0.19 | 25 (6) | 11–40% | 0.20 (0.14) |
| | BDI-II[b] | 13.17 (8.91) | 7.92 (5.69) | 24 | <0.01* | 50 (12) | 33–67% | 0.59 (0.16) |
| | STAI-State[b] | 36.78 (10.33) | 33.48 (7.98) | 23 | 0.03* | 42 (10) | 25–58% | 0.34 (0.14) |
| | STAI-Trait[b] | 37.78 (10.73) | 35.92 (9.10) | 24 | 0.17 | 0 (0) | 0 | −0.02 (0.01) |
| | POMS-Conf[b] | 10.79 (5.05) | 7.17 (3.81) | 24 | <0.01* | 63 (15) | 46–79% | 0.71 (0.17) |
| | POMS-Ten[b] | 10.96 (6.08) | 9.38 (5.88) | 24 | 0.09 | 33 (8) | 18–49% | 0.26 (0.15) |
| | POMS-Depr[b] | 12.38 (10.36) | 7.67 (7.45) | 24 | <0.01* | 46 (11) | 29–63% | 0.45 (0.10) |
| | POMS-Ang[b] | 8.63 (7.90) | 5.83 (6.07) | 24 | <0.01* | 42 (10) | 25–58% | 0.35 (0.11) |
| | FACT-G | 76.95 (14.58) | 82.33 (13.89) | 24 | 0.03* | 29 (7) | 20–44% | 0.37 (0.16) |
| | FACT-BR | 47.42 (11.61) | 52.29 (10.76) | 24 | 0.01* | 38 (9) | 21–54% | 0.42 (0.13) |
| | FACT-TOT | 124.37 (23.87) | 134.71 (22.57) | 24 | <0.01* | 38 (9) | 21–54% | 0.43 (0.13) |

*T1* Pre-stimulant treatment assessment, *T2* Post-stimulant treatment assessment, *RCI + PE* Practice effect adjusted Reliable Change Index for cognitive tests, *MID* Minimally Important Difference (based on 0.5 SD) for symptom measures. *SD* Standard deviation. Abbreviations of tests/measures: see Table 1

[1] Raw scores were converted to standardized Z-scores based on published normative data

[2] Raw scores are shown for the symptom measures

[3] Binomial testing was used for cognitive scores; 90% confidence interval was determined for symptom scores

[a] For cognitive tests: mean differences in Z-scores, For symptom measures: individual change scores divided by total group baseline

[b] Higher score indicates evaluated as worse

* $P < .05$

suggested that for Dig-Span the MPH group remained stable, while the MOD group declined. For TMTA, the MOD group improved while the MPH group remained stable or declined slightly. There were no statistically significant differences in symptom scores over time between the two groups (Table 4).

## Individual improvement after MPH and MOD treatment

There were no differences between the two stimulant groups in the proportion of patients that had a RCI + PE improvement on the cognitive tests, or a MID improvement on the symptom measures (Table 4).

## Change in cognitive scores between lowest- versus higher-performers at baseline

Since recent research suggested that both MPH and MOD may be more efficacious in participants with greater cognitive impairment [11, 37, 38], *T* tests were conducted to examine the differences in cognitive change scores for the quartile of cases with the lowest scores at baseline, versus the three quartiles of cases with higher performance

combined, for each specific cognitive measure. Patients with low baseline evidenced greater improvement on TMT-B only ($P < .001$).

## Discussion

Following a fixed dose of stimulant treatment, patients with PBT improved on tests of speed of processing and executive function requiring divided attention (Dig-Sym and TMTB, respectively).

Comparisons between MPH and MOD treatment did not demonstrate a statistically significant difference in rates of individual, clinically significant improvement (based on RCI + PE criteria) on any cognitive test. Individual improvement was most frequent on a test of executive function requiring divided attention (TMTB) with improvement rates of 28 and 50% for MPH and MOD, respectively.

Analysis of mean score changes over time yielded different patterns of treatment effect for tests of attention span (Dig-Span) and speed of information processing (TMTA). However, at the individual level, there was no clinically significant improvement in attention span for any patient in either group based on the RCI + PE criteria; and only one patient in the MPH group, and none in the MOD group, demonstrated clinically significant improvement in speed of processing. Interpretation of these results is difficult given the inconsistency in these outcomes, which may be heavily influenced by the small sample sizes.

With regard to patient-reported outcomes, patients reported improvements in fatigue, mood, nearly all affective symptoms measured, and quality of life following stimulant treatment, but not in sleep disturbance, tension-anxiety and STAI trait anxiety. Comparisons of either group means or proportions of MID between MOD and MPH treatment did not demonstrate statistically significant differences on any symptom outcome or quality of life scale. Regardless of treatment arm, greater than 40% of patients demonstrated MID-based improvement in fatigue, mood and various affective symptoms. Over 40% of patients treated with MPH additionally reported improvement in vigor-activity and brain-related quality of life, while over 40% of patients treated with MOD reported improved tension-anxiety and general quality of life.

A significant limitation of this study is its small sample size, due to accrual difficulties and a large proportion of drop-outs, which complicates the interpretation of the results of the analyses. Accrual to the study was challenging as many physicians have already incorporated the use of stimulants into their routine practice. Additionally, the 1 month follow-up was earlier than patient's typical follow-up with their physician requiring them to make an additional visit to the hospital. Due to slow accrual the trial was terminated early.

The absence of a placebo control group does not allow us to rule out non-specific treatment effects as an explanation for the observed improvements after stimulant treatment. Improvement in cognitive test performance may also be partly due to practice effects. However, we employed tests with alternate forms whenever possible to minimize this and we used a practice effect adjusted reliable change index (RCI + PE). In fact, this approach yielded somewhat less statistical significant total group results than the group mean approach. Furthermore, practice and nonspecific treatment effects are unlikely to play a major role in the treatment group comparisons, as such effects should be similar for both groups.

When this study was initiated it was expected that, based on their presumably different mechanisms of action, MPH and MOD would result in differential patterns of cognitive improvement. Recently, the mechanisms of action of these drugs were found to share many similarities including impact on dopamine and norepinephrine pathways [9, 13, 14]. In addition to the small sample sizes, this may in part account for the lack of consistent differences between treatments.

The results of this study were based on fixed, moderate doses of MPH and MOD, and may not generalize to higher doses of these stimulants. Notably, although Meyers et al. [18] previously reported beneficial effects associated with MPH at 10 mg twice-daily, they used a dose escalation design with each patient individually balancing efficacy against toxicity that resulted in some patients receiving doses of 30 mg twice-daily.

Recent studies have also suggested that MPH and MOD may be more efficacious in participants with greater impairment at baseline [11, 37, 38], which may be associated with lower plasma levels of dopamine and norepinephrine [38]. In our study we observed that for TMTB only, the measure with the strongest evidence of improvement, the lowest-functioning quartile improved significantly more after stimulant treatment than the other 75%.

This study provides some encouraging evidence of a potential benefit for stimulant therapy on cognition and symptoms (especially fatigue) in PBT patients. Additional studies appear warranted to reach more definitive conclusions. Preliminary evidence suggests that patients with greater objective impairment in cognition may be the optimal candidates for these interventions. However, the precise degree of impairment remains to be determined. Additionally, future studies may wish to target fatigue, changes in measures of processing speed and executive function requiring divided attention, and consider exploring different doses of stimulants within this population.

**Table 4** Comparative effects of MPH and MOD treatment on cognitive tests and symptom measures: analyses of differences in group means and frequency of improvement

| | | T1 MPH | T2 MPH | Sample size MPH | T1 MOD | T2 MOD | Sample size MOD | RM-ANCOVA | RCI + PE / MID improvement | | Fisher's exact |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Measure | Mean (SD) | Mean (SD) | *N* | Mean (SD) | Mean (SD) | *N* | *P* | MPH % (N) | MOD % (N) | *P* |
| Cognitive tests[1] | Dig-Span | −0.29 (1.25) | −0.31 (1.20) | 19 | −0.27 (0.86) | −0.67 (1.13) | 5 | 0.05* | 0 (0) | 0 (0) | N/A |
| | Dig-Sym | −0.79 (1.05) | −0.42 (1.25) | 19 | −1.13 (1.27) | −1.13 (1.57) | 5 | 0.29 | 11 (2) | 0 (0) | 1.00 |
| | TMTA | −1.16 (3.04) | −2.10 (6.72) | 19 | −5.25 (4.34) | −3.71 (4.11) | 4 | 0.05* | 5 (1) | 0 (0) | 1.00 |
| | TMTB | −3.29 (7.56) | −0.74 (2.95) | 18 | −7.67 (7.34) | −5.81 (6.62) | 4 | 0.27 | 28 (5) | 50 (2) | 0.56 |
| | HVLT-R IR | −1.24 (2.10) | −1.17 (2.15) | 18 | −2.78 (1.94) | −3.13 (1.86) | 5 | 0.30 | 6 (1) | 0 (0) | 1.00 |
| | HVLT-R DR | −1.19 (2.04) | −0.89 (2.02) | 18 | −4.02 (2.53) | −3.34 (2.99) | 5 | 0.65 | 0 (0) | 0 (0) | N/A |
| | HVLT-R DRecog | −0.52 (1.23) | −0.89 (1.71) | 18 | −0.56 (1.37) | −2.55 (1.30) | 5 | 0.16 | 6 (1) | 0 (0) | 1.00 |
| | COWA | −0.46 (1.26) | −0.72 (1.19) | 18 | −0.89 (0.89) | −1.48 (0.67) | 5 | 0.20 | 0 (0) | 0 (0) | N/A |
| | Peg-D | −2.72 (3.43) | −3.02 (6.46) | 19 | −8.80 (12.35) | −9.71 (12.70) | 5 | 0.55 | 11 (2) | 0 (0) | 1.00 |
| | Peg-ND | −1.90 (2.04) | −1.74 (2.65) | 19 | −6.36 (11.41) | −0.82 (2.68) | 3 | 0.82 | 16 (3) | 0 (0) | 1.00 |
| Symptom measures[2] | BFI Total[a] | 37.84 (21.61) | 28.84 (17.20) | 19 | 49.40 (21.17) | 45.60 (23.65) | 5 | 0.18 | 42 (8) | 60 (3) | 0.63 |
| | POMS-Fat[a] | 12.95 (6.86) | 8.58 (6.24) | 19 | 15.40 (5.03) | 10.80 (7.46) | 5 | 0.77 | 53 (10) | 40 (2) | 1.00 |
| | POM-Vig | 13.68 (7.56) | 16.42 (7.09) | 19 | 12.20 (9.26) | 13.00 (7.18) | 5 | 0.32 | 53 (10) | 20 (1) | 0.33 |
| | BSDS Sleep[a] | 21.79 (12.28) | 19.00 (9.06) | 19 | 25.60 (7.02) | 25.20 (9.20) | 5 | 0.24 | 26 (5) | 20 (1) | 1.00 |
| | BDI-II[a] | 13.32 (8.59) | 8.16 (5.73) | 19 | 12.60 (11.15) | 7.00 (6.08) | 5 | 0.72 | 53 (10) | 40 (2) | 1.00 |
| | STAI-State[a] | 36.68 (10.63) | 33.08 (7.27) | 19 | 37.25 (10.21) | 35.00 (11.18) | 4 | 0.80 | 42 (8) | 40 (2) | 1.00 |
| | STAI-Trait[a] | 38.45 (11.54) | 36.42 (9.79) | 19 | 35.20 (7.22) | 34.00 (6.20) | 5 | 0.94 | 0 (0) | 0 (0) | N/A |
| | POMS-Conf[a] | 10.84 (5.17) | 7.00 (3.82) | 19 | 10.60 (5.13) | 7.80 (4.15) | 5 | 0.59 | 68 (13) | 40 (2) | 0.33 |
| | POMS-Ten[a] | 10.95 (6.75) | 10.11 (6.25) | 19 | 11.00 (2.74) | 6.60 (3.29) | 5 | 0.09 | 26 (5) | 60 (3) | 0.29 |
| | POMS-Depr[a] | 13.05 (11.58) | 8.42 (8.06) | 19 | 9.80 (1.79) | 4.80 (3.70) | 5 | 0.40 | 42 (8) | 60 (3) | 0.63 |
| | POMS-Ang[a] | 9.11 (8.55) | 6.21 (6.70) | 19 | 6.80 (4.92) | 4.40 (2.61) | 5 | 0.86 | 42 (8) | 40 (2) | 1.00 |
| | FACT-G | 76.62 (14.55) | 82.16 (12.73) | 19 | 78.20 (16.32) | 83.00 (19.47) | 5 | 0.98 | 21 (4) | 60 (3) | 0.27 |
| | FACT-BR | 47.42 (10.63) | 52.68 (9.83) | 19 | 47.40 (16.32) | 50.80 (15.06) | 5 | 0.61 | 42 (8) | 20 (1) | 0.61 |
| | FACT-TOT | 124.04 (22.40) | 134.95 (19.72) | 19 | 125.60 (31.88) | 133.80 (34.30) | 5 | 0.76 | 37 (7) | 40 (2) | 1.00 |

*T1* Pre-stimulant treatment assessment, *MPH* methylphenidate (IR + SR), *T2* Post-stimulant treatment assessment, *MOD* modafinil, *RM-ANCOVA* Repeated measures analysis of covariance, *RCI + PE* Practice effect adjusted Reliable Change Index for cognitive tests, *MID* Minimally Important Difference (based on 0.5 SD) for symptom measures, *SD* Standard deviation, *N/A* Not applicable (no improvers), Abbreviations of measures: see Table 1

[1] Raw scores were converted to standardized Z-scores based on published normative data

[2] Raw scores are shown for the symptom measures

[a] Higher score indicates evaluated as worse

* $P < .05$

## References


1. Taphoorn MJ, Klein M (2004) Cognitive deficits in adult patients with brain tumours. Lancet Neurol 3:159–168
2. Gehring K, Aaronson NK, Taphoorn MJ, Sitskoorn MM (2010) Interventions for cognitive deficits in patients with a brain tumor: an update. Exp Rev Anticancer Ther 10:1779–1795. doi:10.1586/era.10.163
3. Volkow ND, Fowler JS, Wang G, Ding Y, Gatley SJ (2002) Mechanism of action of methylphenidate: insights from PET imaging studies. J Atten Disord 6(Suppl 1):S31–S43
4. Hannestad J, Gallezot JD, Planeta-Wilson B, Lin SF, Williams WA, van Dyck CH, Malison RT, Carson RE, Ding YS (2010) Clinically relevant doses of methylphenidate significantly occupy norepinephrine transporters in humans in vivo. Biol Psych 68:854–860. doi:10.1016/j.biopsych.2010.06.017
5. Berridge CW, Devilbiss DM (2011) Psychostimulants as cognitive enhancers: the prefrontal cortex, catecholamines, and attention-deficit/hyperactivity disorder. Biol Psychiatry 69:e101–e111. 10.1016/j.biopsych.2010.06.023
6. Auriel E, Hausdorff JM, Giladi N (2009) Methylphenidate for the treatment of Parkinson disease and other neurological disorders. Clin Neuropharmacol 32:75–81. doi:10.1097/WNF.0B013E318170576C
7. Siddall OM (2005) Use of methylphenidate in traumatic brain injury. Ann Pharmacother 39:1309–1313. doi:10.1345/aph.1E637
8. Repantis D, Schlattmann P, Laisney O, Heuser I (2010) Modafinil and methylphenidate for neuroenhancement in healthy individuals: a systematic review. Pharmacol Res 62:187–206. doi:10.1016/j.phrs.2010.04.002
9. Volkow ND, Fowler JS, Logan J, Alexoff D, Zhu W, Telang F, Wang GJ, Jayne M, Hooker JM, Wong C, Hubbard B, Carter P, Warner D, King P, Shea C, Xu Y, Muench L, Apelskog-Torres K (2009) Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. JAMA 301:1148–1154. doi:10.1001/jama.2009.351
10. Turner DC, Robbins TW, Clark L, Aron AR, Dowson J, Sahakian BJ (2003) Cognitive enhancing effects of modafinil in healthy volunteers. Psychopharmacol (Berl) 165:260–269. doi:10.1007/s00213-002-1250-8
11. Muller U, Steffenhagen N, Regenthal R, Bublak P (2004) Effects of modafinil on working memory processes in humans. Psychopharmacol (Berl) 177:161–169. doi:10.1007/s00213-004-1926-3
12. Walsh JK, Randazzo AC, Stone KL, Schweitzer PK (2004) Modafinil improves alertness, vigilance, and executive function during simulated night shifts. Sleep 27:434–439
13. Young JW, Geyer MA (2010) Action of modafinil–increased motivation via the dopamine transporter inhibition and D1 receptors? Biol Psychiatry 67:784–787. doi:10.1016/j.biopsych.2009.12.015
14. Minzenberg MJ, Watrous AJ, Yoon JH, Ursu S, Carter CS (2008) Modafinil shifts human locus coeruleus to low-tonic, high-phasic activity during functional MRI. Science 322:1700–1702. doi:10.1126/science.1164908
15. Brown JN, Howard CA, Kemp DW (2010) Modafinil for the treatment of multiple sclerosis-related fatigue. Ann Pharmacother 44:1098–1103. doi:10.1345/aph.1M705
16. Cooper MR, Bird HM, Steinberg M (2009) Efficacy and safety of modafinil in the treatment of cancer-related fatigue. Ann Pharmacother 43:721–725. doi:10.1345/aph.1L532
17. Weitzner MA, Meyers CA, Valentine AD (1995) Methylphenidate in the treatment of neurobehavioral slowing associated with cancer and cancer treatment. J Neuropsyc Clin Neurosci 7:347–350
18. Meyers CA, Weitzner MA, Valentine AD, Levin VA (1998) Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. J Clin Oncol 16:2522–2527
19. Kaleita TA, Wellisch DK, Graham CA, Steh B, Nghiemphu P, Ford JM, Lai A, Peak S, Cloughesy TF (2006) Pilot study of modafinil for treatment of neurobehavioral dysfunction and fatigue in adult patients with brain tumors. J Clin Oncol 24:1503
20. 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 (2007) 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 69:1496–1501
21. Minton O, Richardson A, Sharpe M, Hotopf M, Stone PC (2011) Psychostimulants for the management of cancer-related fatigue: a systematic review and meta-analysis. J Pain Symptom Manage 41:761–767. doi:10.1016/j.jpainsymman.2010.06.020
22. Portela MA, Rubiales AS, Centeno C (2011) The use of psychostimulants in cancer patients. Curr Opin Support Palliat Care 5:164–168. doi:10.1097/SPC.0b013e3283462ff3
23. Lasheen W, Walsh D, Mahmoud F, Davis MP, Rivera N, Khoshknabi DS (2010) Methylphenidate side effects in advanced cancer: a retrospective analysis. Am J Hosp Palliat Care 27:16–23. doi:10.1177/1049909109345145
24. Fernandez F, Adams F (1986) Methylphenidate treatment of patients with head and neck cancer. Head Neck surg 8:296–300
25. Bruera E, Miller MJ, Macmillan K, Kuehn N (1992) Neuropsychological effects of methylphenidate in patients receiving a continuous infusion of narcotics for cancer pain. Pain 48:163–166
26. Gagnon B, Low G, Schreier G (2005) Methylphenidate hydrochloride improves cognitive function in patients with advanced cancer and hypoactive delirium: a prospective clinical study. J psychiatry Neurosci 30:100–107
27. Mar Fan HG, Clemons M, Xu W, Chemerynsky I, Breunis H, Braganza S, Tannock IF (2008) A randomised, placebo-controlled, double-blind trial of the effects of d-methylphenidate on fatigue and cognitive dysfunction in women undergoing adjuvant chemotherapy for breast cancer. Support Care Cancer 16:577–583. doi:10.1007/s00520-007-0341-9
28. Kohli S, Fisher SG, Tra Y, Adams MJ, Mapstone ME, Wesnes KA, Roscoe JA, Morrow GR (2009) The effect of modafinil on cognitive function in breast cancer survivors. Cancer 115:2605–2616. doi:10.1002/cncr.24287
29. Lundorff LE, Jonsson BH, Sjogren P (2009) Modafinil for attentional and psychomotor dysfunction in advanced cancer: a double-blind, randomised, cross-over trial. Palliat Med 23:731–738. doi:10.1177/0269216309106872
30. Blackhall L, Petroni G, Shu J, Baum L, Farace E (2009) A pilot study evaluating the safety and efficacy of modafinal for cancer-related fatigue. J Palliat Med 12:433–439. doi:10.1089/jpm.2008.0230
31. Chelune GJ, Naugle RI, Luders H, Sedlak J, Awad IA (1993) Individual change after epilepsy surgery: practice effects and base-rate information. Neuropsychology 7:41–52
32. Wechsler D (1997) Wechsler adult intelligence scale III. Psychological Corporation, San Antonio
33. Benedict RH, Zgaljardic DJ (1998) Practice effects during repeated administrations of memory tests with and without alternate forms. J Clin Exp Neuropsychol 20:339–352
34. Ruff R, Light R, Parker S (1996) Visuospatial learning: ruff light trail learning test. Arch Clin Neuropsychol 11:313–327
35. Levine AJ, Miller EN, Becker JT, Selnes OA, Cohen BA (2004) Normative data for determining significance of test-retest differences on eight common neuropsychological instruments. Clin Neuropsychol 18:373–384
36. Norman GR, Sloan JA, Wyrwich KW (2003) Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 41:582–592. doi:10.1097/01.MLR.0000062554.74615.4C

37. Randall DC, Shneerson JM, File SE (2005) Cognitive effects of modafinil in student volunteers may depend on IQ. Pharmacol Biochem Behav 82:133–139. doi:10.1016/j.pbb.2005.07.019

38. Finke K, Dodds CM, Bublak P, Regenthal R, Baumann F, Manly T, Muller U (2011) Effects of modafinil and methylphenidate on visual attention capacity: a TVA-based study. Psychopharmacol (Berl) 210:317–329. doi:10.1007/s00213-010-1823-x