Assessment of the Efficacy of Immediate Release Methylphenidate, Sustained Release Methylphenidate, and Modafinil for Patients with Primary Brain Tumor

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Introduction

- Impaired neurocognitive function (NCF) is common in primary brain tumor (PBT) patients and may reflect the effects of tumor burden and treatment.
- NCF is an important aspect of quality of life (QOL). Impaired NCF has been associated with diminished QOL.
- Treatmet of neurocognitive descline frequently involves the use of psychostimulants such as methylphenidate, d-threo-methylphenidate HCL, dextroamphetamine, and pemoline.
- Mechanism of action of psychostimulants includes countering the effects of disease x treatment x patient factors on the monoamine pathways in the frontal—brainstem system (including the RAS) (Iversen, 1975; Simon et al., 1980).
- Psychostimulants have been reported to reduce fatigue and depression (consistent with monoamine hypothesis of depression) among cancer patients (Breitbart & Mermelstein,1992; Burns & Eisendrath,1994; Fernandez et al.,1986,1987; Olin & Masand,1996; Weitzner et al.,1995).
- However, limited research is available regarding the efficacy of immediate release methylphenidate (IRM) in treating NCF and QOL impairment among PBT patients (Thompson, Leigh, Christensen et al., 2001; Weitzner, Meyers, Valentine, et al., 1995, 1997, 1998; Delong et al., 1992). Available data show that IRM leads to improvements in NCF and neurobehavioral function among PBT patients. Evidence for improvement in QOL is equivocal.
- There is a lack of research assessing the efficacy of sustained release methylphenidate (SRM) and of other stimulants such as the novel vigilance enhancing drug modafinil in treating impaired NCF among PBT patients.
- The objective of this trial was to compare IRM with SRM and modafinil for the improvement of NCF of PBT patients. It was expected that patients receiving methylphenidate would demonstrate differential improvement on tests of memory, executive function and psychomotor processing speed relative to patients treated with modafinil, while patients receiving modafinil would exhibit differential improvement on tests of attention measures.

Methods

- We conducted a two arm, open-label, pilot study comparing the efficacy of IRM, SRM, and modafinil as treatment of NCF dysfunction and fatigue among PBT patients.
- Twenty-four PBT patients were identified by their treating neuro-oncologit if they were considering treatment with a psychostimulant. Patients were randomly assigned to each of the three groups: IRM (ritalin), SRM (concerta), and modafinil (provigil).
- Patients received ritalin 10 mg, concerta 18 mg, or modafinil 200 mg for 4 weeks (mean duration = 33 days).
- Assessment of NCF and QOL was performed before and after 4 weeks of stimulant therapy.
- **Statistical Analyses:** Pre-treatment versus post-treatment changes in the NCF performance were analyzed using standardized scores. Raw/standardized scores were used for fatigue, symptom, and QOL measures. The likelihood ratio statistic, controlling for baseline performance and adjustment for multiple comparisons, was used to measure longitudinal changes in NCF. The practice effect adjusted reliable change index (RCI+PE) was also calculated for NCF measures and was used to determine the frequency of "clinically significant" change.

Neurocognitive Tests Grouped by Domain

Domain	Neurocognitive Test
Attention	WAIS-III Digit Span (DS)
Processing Speed	Trail Making Test—Part A (TMTA) WAIS-III Digit Symbol (DSym)
Memory	Hopkins Verbal Learning Test—Revised (HVLT—R) Trials 1-3 (HVLT-R 1-3) Delayed Recall (HVLT-R-DR) Delayed Recognition (HVLT-R DRecog)
Executive Function	Trail Making Test—Part B (TMTB) Controlled Oral Word Association (COWA)
Motor Dexterity	Lafayette Grooved Pegboard Dominant (Peg-D) Non-Dominant (Peg-ND)

QOL, Mood and Symptom Measures

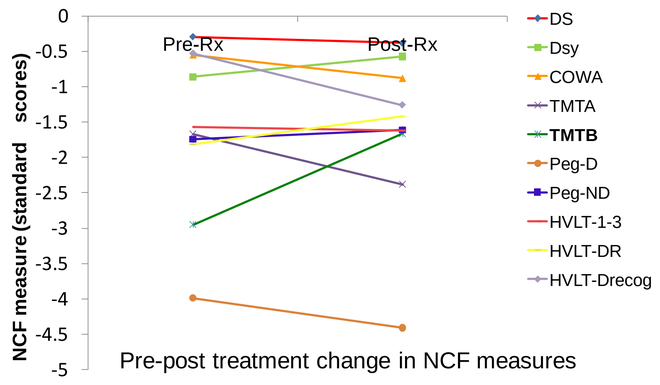
Domain	Self-Report Measure
QOL	Functional Assessment of Cancer Therapy with Brain Module (FACT-BR)
Fatigue	Brief Fatigue Inventory (BFI)
Sleep	Brief Sleep Disturbance Scale (BSDS)
Mood	Profile of Mood States (POMS)
Depression	Beck Depression Inventory–II (BDI–II)

Demographic and Clinical Characteristics

Variable	N = 24
Age (Years: Mean ± SD)	44.96 ± 10.82
Education (Years: Mean ± SD)	14.46 ± 2.34
Gender (% Female)	46%
Ethnicity (% Caucasian)	96%
Handedness (% Right)	96%
Tumor Location (%)	
Left	52%
Right	48%

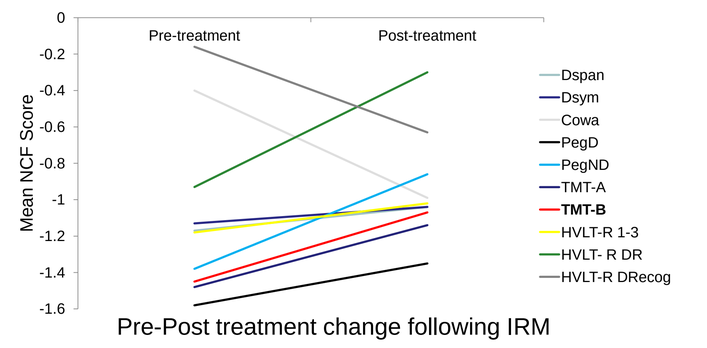
Results

Mean NCF Before and After Stimulant Treatment

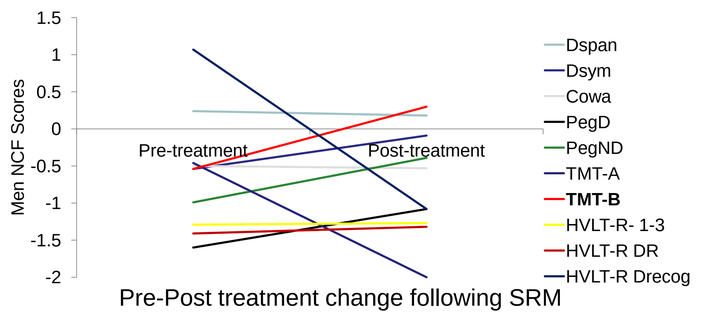


Pre-post treatment change in NCF measures

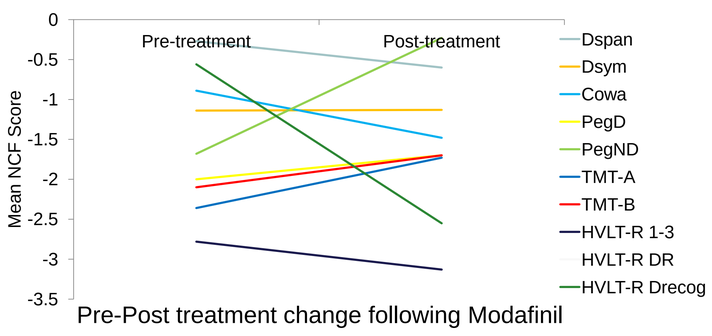
Mean NCF Before and After by Treatment Type



Pre-Post treatment change following IRM



Pre-Post treatment change following SRM



Pre-Post treatment change following Modafinil

Longitudinal Changes in NCF Following Stimulant Therapy

Domain	NCF Test	X^2 statistic
Attention	DS	2.96
Processing Speed	TMTA	1.41
	DSym	0.89
Memory	HVLT 1-3	0.34
	HVLT DR	0.18
	HVLT Recog	0.16
Executive Function	TMTB*	2.96
	COWA	0.23
Motor Dexterity	Peg-D	7.04
	Peg-ND	1.41

* Significant difference at $p = 0.001$

Longitudinal Changes in QOL Following Stimulant Therapy

Domain	QOL measure	X^2 statistic
QOL	FACT-G	0.048
	FACT-BR	0.002
Fatigue	BFI	0.398
Sleep	BSDS	2.376
Mood	POMS-VA	1.068
	POMS-FI	0.04
Depression	BDI—II	0.064

Frequency of RCI+PE Determined Change in NCF Following Stimulant Therapy

Domain	NCF Test	Improve (%)	Stable (%)	Decline (%)
Attention	DS	0	92	8
Processing Speed	TMTA	4	74	22
	DSym	8	84	8
Memory	HVLT 1-3	4	87	9
	HVLT DR	4	96	0
	HVLT Recog	0	70	30
Executive Function	TMTB	36	59	5
	COWA	0	83	17
Motor Dexterity	Peg-D	12	75	13
	Peg-ND	14	64	22

Discussion

- TMTB showed substantial clinical improvement (36% patients improved) upon stimulant treatment. Particularly, those in IRM group showed remarkable post-treatment gains on TMTB.
- No other substantial clinical changes were noticeable.
- Longitudinal analyses comparing methylphenidate with modafinil showed that patients receiving methylphenidate (slope = 2.017) demonstrated greater statistical improvement than patients receiving modafinil (slope=0.975) on TMTA (chi-square statistic (df = 1) = 10.272, p = 0.001).
- There were no statistically significant changes on longitudinal analyses of mood, fatigue, and QOL measures.
- Overall, methylphenidate improved psychomotor processing speed but did not result in differential change on memory or executive function measures.
- Modafinil did not demonstrate differential effects on measures of attention.