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METHYLPHENIDATE SIDE EFFECTS IN ADVANCED CANCER: A RETROSPECTIVE ANALYSIS

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Abstract

Introduction—Methylphenidate (MP) is often recommended for symptom control in advanced cancer. Little is known about its side effects in frail adults.

Objectives—To evaluate MP associated symptoms or side effects (S/E) in three symptom studies among patients with advanced cancer.

Methods—Data was collected from two published prospective cohort series and a phase 2 study of MP for symptom control in advanced cancer. All three reports had identical dosing schedules and symptom assessments. Initial MP doses were 10 mg/d (5 mg at 8 a.m. and at 12 noon) titrated up to a maximum of 30 mg/d. Depression, fatigue, and symptoms identified as possible MP S/E (agitation, anorexia, dizziness, dry mouth, headache, insomnia, nausea, palpitation, tremors, vomiting) were evaluated for presence (prevalence) and for severity (using categorical scales) before MP (day 0) and on days 3, 5 and 7 thereafter. The categorical scale used was none, mild, moderate, and severe. For this analysis all who received at least one dose of MP were evaluable for potential S/E, and those who completed 7 consecutive days therapy were evaluable for efficacy.

Results—62 patients were enrolled. 50 completed 7 days of MP with a median age of 69 (range 30–90) years. Thirty-five received MP 10 mg/day, one 15 mg/day, thirteen 20 mg/day, and one 30 mg/d of MP by day 7. Most (96 %) had improvement in depression and/or fatigue. Amongst the 62 patients new symptom prevalence throughout the study was; agitation (16%), insomnia (16%), dry mouth (15%), nausea (10%), tremors (6%), anorexia (5%), headache (3%), palpitations (2%), and vomiting (2%). Patients could have more than one symptom simultaneously. Seven patients (11%) withdrew due to MP S/E. Moderate symptoms occurred in 10 people during the study period, but none had severe symptoms. Some symptoms present before MP showed significant improvement during MP therapy; agitation [0.48 ± 0.68 to 0.32 ± 0.55 ($P < 0.029$)], anorexia [0.86 ± 1.00 to 0.67 ± 0.83 ($P < 0.008$)], and dizziness [0.14 ± 0.40 to 0.06 ± 0.31 ($P < 0.011$)].

Conclusions—1) Treatment with MP (10–20 mg/d) in advanced cancer is well tolerated; only 11% withdrew due to MP S/E. 2) S/E symptoms occurring with MP appeared to improve

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spontaneously despite continued MP therapy. The commonest new symptoms after MP started were agitation (16%), insomnia (16%), and dry mouth (15%). 3) Depression and fatigue improved at doses lower than those recommended in other clinical conditions. 4) MP improved depression and fatigue, and some secondary symptoms associated with them. Methylphenidate (MP) appears safe when used in the treatment of depression and fatigue in advanced cancer.

INTRODUCTION

Methylphenidate (MP: Ritalin©, Novartis, East Hanover, NJ) is a central nervous system (CNS) stimulant structurally related to amphetamine. It is a competitive blocker of dopamine transporters, and to a lesser extent norepinephrine and serotonin transporters. Therapeutic levels enhance extracellular dopamine levels in basal ganglia, pre-frontal cortex, as well as other sites.^{1,2,3} MP is a racemate with d-threo-MP as the active enantiomer.^{1,2} It is well absorbed from the gastrointestinal tract; food enhances absorption. As a rule, we prescribe divided doses before meals in the morning and at noon to avoid insomnia and hopefully avoid side-effects from too rapid absorption.^{4,5,6} Peak plasma concentrations occur one to three hours after administration and drug half-life is about two hours..¹

MP has been used in clinical practice mainly for attention deficit hyperactivity disorder (ADHD) in children and narcolepsy in adults. MP may relieve both depression and fatigue in cancer patients.³⁻⁶ Importantly symptoms are relieved quickly in this frail cancer population with apparently few side effects (S/E), and rarely any drug interactions.¹ However the literature regarding MP safety in individuals without cancer may not be applicable in advanced cancer, since most studies have involved otherwise healthy children with ADHD. In addition symptoms occurring due to cancer progression, and S/E associated with medications common in advanced diseases (such as opioids) may be similar to MP S/E and difficult to differentiate. We therefore evaluated possible MP S/E in advanced cancer by examining new symptoms which developed after the introduction of MP. We did this in pooled data from two case series, and one Phase 2 study to determine the safety of MP in advanced cancer patients.

METHODS

Background

Symptoms that might be identified as MP S/E were identified by reviewing the literature and various standard pharmacologic texts. Possible MP S/E were collected from two previously published case series and a Phase 2 trial. One case series involved ten hospice patients treated for depression.⁴ Another was a series of eleven with advanced cancer treated for fatigue.⁵ In the Phase 2 study, 41 cancer patients with depression were enrolled.⁶ All three reports used a similar advanced cancer patient population, and identical dosing schedules and symptom assessments (Figure 1); therefore it was reasonable to pool the symptom data.

Symptoms of depression and fatigue and possible S/E symptoms attributable to MP use (agitation, anorexia, dizziness, dry mouth, headache, insomnia, nausea, palpitation, tremors, vomiting) were evaluated using a standardized symptom checklist at baseline (day 0) before MP and on days 3, 5, and 7 thereafter via telephone or bedside interview. Symptoms were assessed using a categorical scale (none (0), mild (1), moderate (2), and severe (3), respectively).

Lack of response for either fatigue or depression, and the absence of dose limiting symptoms by day 3, and then day 5 were indications to titrate the MP dose. MP was started at 10 mg/day (5 mg at 8 a.m. and at 12 noon) on day 1. The dose was increased from 5mg to 10 mg to

15 mg twice a day as indicated. The maximum allowable total daily dose was 30 mg / day. If a response was noted the same dose was continued. Treatment was discontinued after one week if no improvement in the primary target symptoms was seen at the maximum dose, or if significant new symptoms developed which could reasonably be identified as MP S/E without relief of fatigue or depression. For this analysis all who received at least one dose of MP were evaluable for new S/E symptoms, and those who completed 7 days were evaluable for efficacy.

Statistical Analysis

Continuous variables are summarized as the mean, standard deviation, median, and range. Categorical variables are summarized as frequency counts and percentages; percentages were rounded to the nearest whole number. To describe symptom severity, a numerical value of 0, 1, 2, and 3 were assigned to none, mild, moderate, and severe symptoms, respectively. The mean scores were computed for each symptom at each follow up day, and the Mantel-Haenszel correlation statistic was used to determine change in mean scores of symptom severity over time. SAS® statistical software was used to analyze the data (SAS Institute, Inc., Cary, NC). A P value < 0.05 was considered significant.

RESULTS

Sixty-two patients from 3 studies were evaluable. Seven (11%) were withdrawn from the studies due to distressing new symptoms. Agitation (n=2); agitation and insomnia (n=2); agitation, dry mouth and insomnia (n=1); dysphoria (n=1); and nightmares (n=1) were the reasons for withdrawal. Another three were lost to follow-up, one had MP discontinued on hospital admission, and one refused to continue MP despite absence of S/E. Fifty completed 7 days of MP; demographic data is in Table 1. Forty-eight (96%) had improvement in depression and/or fatigue. Thirty-five (70%) responded at the 10mg/day dose level. Most were maintained on 10 mg/day throughout the study period. On day 7, thirty-five were on 10 mg/d, one 15 mg/d, thirteen 20 mg/d, and one 30 mg/d. Of the 50 who finished seven days of therapy, moderate new symptoms occurred in 10: dry mouth (5), insomnia (2), agitation (1), anorexia (1), and nausea (1). None had severe symptoms. New symptoms developing after MP (N=62) included: agitation (16%), insomnia (16%), dry mouth (15%), nausea (10%), tremors (6%), anorexia (5%), headache (3%), palpitations (2%), and vomiting (2%). Some had more than one new symptom. The mean symptom severity for each evaluation day is in Table 2. Statistically significant improvements in preexisting agitation, anorexia, and dizziness were observed, in addition to less depression and fatigue.

DISCUSSION

In advanced cancer, MP has been used to treat depression, fatigue, opioid-induced sedation, hiccups, to potentiate opioid analgesia, and to improve cognitive function..⁷⁻⁹ MP seems to be well tolerated in advanced disease. Several authors have described the use of MP in cancer patients. Discontinuation due to adverse events is not common, according to our literature search of published prospective studies of adult cancer patients, and there were no differences in dropout rates in placebo controlled trials (Table 3).¹⁰⁻²³ Agitation, confusion, tachycardia, and other S/E were reported in these studies (Table 3). The percentage of patients that discontinued MP due to potential S/E is similar to ours, and is consistently below 20%.

In our analysis any new symptoms that developed after MP were assumed to imply MP S/E. However, disease progression can cause symptoms similar to MP S/E, and this complicated toxicity assessment. Tolerance to MP S/E may develop with sustained exposure (similar to nitroglycerin for angina).²⁴ Continuous drug exposure with sustained release MP may lead

to tachyphylaxis to S/E, which means that S/E maybe transient and missed if assessment is infrequent.²⁴ Currently, there is a new formulation of MP, an extended-release form, (OROS-MP or Concerta™. Alza Corp. of Mountain View, California USA). This product has a rapid onset of action (1-2 hours) and long duration of efficacy (10-12 hours) in ADHD children after a single administration in the morning.²⁴ Its benefit in this population equals that of normal-release formulations, but with greater compliance. Sustained release MP may or may not have the same benefits as normal release MP in advanced cancer and this should be subject for future study.

In this study seven (11%) out of sixty two patients withdrew due to presumed MP adverse events (agitation, dysphoria, insomnia, nightmares). These events can reasonably be attributable to MP S/E given its pharmacology and the nature of the symptoms. Intuitively debilitated patients should be at greatest risk of drug side effects. But only 10 had new symptoms rated as moderate (dry mouth, insomnia); and none experienced new severe symptoms. Insomnia was the commonest new symptom despite the dose schedule at 8 a.m. and 12 noon. Single dose MP at 8 a.m. rather than divided between 8 a.m. and 12 noon might reduce insomnia, though there is no data to support this.

MP improved cognitive impairment and hypoactive delirium in advanced cancer without increased seizure frequency.^{17,21} In our analysis, improved agitation, anorexia, and dizziness (present before MP administration) were also observed. This was surprising; worse agitation and anorexia would have been anticipated based on the pharmacology of MP, and reports of MP in ADHD and narcolepsy. The improvement in those symptoms might be secondary to less agitated depression and/or improved fatigue. It is noteworthy that these symptoms were not routinely monitored before and after MP administration in most prior studies of MP in advanced cancer.

In our studies depression and fatigue improved in most patients at doses lower than recommended in other clinical conditions. Adult MP doses necessary to block 50% of dopamine transporters (required for response) are usually 0.25 mg/kg or 17.5 milligrams total daily dose. Therefore most patients would be anticipated to require greater than 10 mg per day for response.²⁴ Our research supports the therapeutic benefit of MP at lower doses. Recently a placebo-controlled trial demonstrated improvement in fatigue a week after starting MP treatment.¹⁴ This improvement was not superior to placebo when fatigue intensity was assessed using FACIT-F and ESAS scales, but superior when using a subjective improvement scale; 46% in the MP group reported moderate or severe benefit, versus 27% in the placebo group; a significant difference. Perhaps the psychometric properties of fatigue assessment instruments should be revisited. Further controlled Phase III trials are still needed.

Psychostimulants appear to be reasonably safe even in those with respiratory insufficiency.²⁵ Although most experience improvement in target symptoms, some will experience worsening symptoms compatible with S/E so it is important to monitor symptom profiles in those on MP. Multiple studies have shown a low risk for MP abuse though caution should be used in those with a history of addiction.¹ The S/E profile with chronic dosing, patient satisfaction, and quality of life were not addressed in most studies and should also serve as areas for future research. The timing of S/E assessment might influence detection of toxicity. Co-administration of drugs as dopamine receptor blockers may also influence response; one study demonstrated antagonistic activities of MP effects and haloperidol in those with ADHD.²⁶

Our data had several disadvantages; separately the studies were not powered to detect side effects; and it was not controlled for placebo effects. However the subjects were

representative of our palliative care cancer population; data was collected using a standardized collection sheet and according to a uniform schedule. Pooled data allowed for a larger sample size to evaluate new symptoms which might reasonably be attributed to MP. Based on our open-label studies 96% responded to MP treatment for the major indication. Positive treatment effects were achieved within 3 days using a low dose (10mg / day) in seventy percent. In addition other secondary symptoms like anorexia were significantly reduced; this might be secondary to improvement in depression, fatigue, or an independent therapeutic effect. This suggests additional multisymptom benefits to MP that needs to be confirmed in future studies.

This analysis has several clinical implications. MP appears to be a safe, effective, medication (and is relatively inexpensive). It apparently palliates multiple symptoms, and may do so simultaneously. It is relatively ideal for those with an expected short survival due to its rapid onset of action (compared to other agents) for depression. As it is cheap MP will benefit those in hospice capitated reimbursement programs. Research should further clarify the benefits in cancer related fatigue, MP effectiveness compared to other antidepressants, the place of MP in opioid related sedation, the influence on quality of life, the beneficial effects on performance status and hospital length of stay. Dose, timing and formulation (sustained release versus normal release) need to be studied further. A randomized trial comparing MP to other antidepressants in advanced cancer would better define MP clinical benefits in advanced cancer.

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Date: _____ Day 0 3 5 7

Patient initials: _____ Methylphenidate dose: _____

CCF #: _____

1. Are you depressed? Have you been feeling down or blue?

☐ Yes ☐ No

(Ask the next on day 3,5,7)

Is your mood ☐ better ☐ worse ☐ the same as before you started the drug?

2. Do you find yourself worrying about little things or worrying excessively?

☐ Yes ☐ No

3. Are you able to experience pleasure?

If something good happens can it help you feel better?

☐ Yes ☐ No

4. Do you cry more easily than usual?

☐ Yes ☐ No

5. Have you been sleeping

☐ more ☐ less ☐ the same as usual

If more or less, is it

☐ mild ☐ moderate ☐ severe

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If insomnia is present, is it: ☐ Initial insomnia

☐ Frequent awakenings during the night

☐ Waking up earlier than you want to

6. Has your appetite

☐ Decreased ☐ increased ☐ the same

If increased or decreased, is it

☐ mild ☐ moderate ☐ severe
(if severe or new onset discuss the issue with the attending physician)

7. Have you been having problems sitting still?

☐ Yes ☐ No If yes, since when _____

Is it ☐ mild ☐ moderate ☐ severe
(if severe or new onset discuss the issue with the attending physician)

8. Have you been feeling tired or worn out?

☐ Yes ☐ No If yes, since when _____

Is it ☐ mild ☐ moderate ☐ severe

9. Have you been having problems thinking or concentrating?

☐ Yes ☐ No If yes, when did it start _____

Is it ☐ mild ☐ moderate ☐ severe

(Ask the next question when the patient is depressed, feeling down or blue)

(The patient is considered to have suicidal ideation if 1 and 2 or 1, 2 and 3 are yes)

10. Have you been having any thoughts about dying? ☐ Yes ☐ No

If yes, Have you thought of taking your life? ☐ Yes ☐ No

If yes, did you think of a way to do it? ☐ Yes ☐ No

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11. How is your pain today?

(no pain) 0 1 2 3 4 5 6 7 8 9 10 (the worst pain)

Side Effects:

Agitation	☐ None	☐ Mild	☐ Moderate	☐ Severe
Anorexia	☐ None	☐ Mild	☐ Moderate	☐ Severe
Dizziness	☐ None	☐ Mild	☐ Moderate	☐ Severe
Dry mouth	☐ None	☐ Mild	☐ Moderate	☐ Severe
Headache	☐ None	☐ Mild	☐ Moderate	☐ Severe
Insomnia	☐ None	☐ Mild	☐ Moderate	☐ Severe
Nausea	☐ None	☐ Mild	☐ Moderate	☐ Severe
Palpitations	☐ None	☐ Mild	☐ Moderate	☐ Severe
Tremors	☐ None	☐ Mild	☐ Moderate	☐ Severe
Vomiting	☐ None	☐ Mild	☐ Moderate	☐ Severe

**(if severe or new onset discuss with the attending physician)*

(Ask this question on day 7)

Are you satisfied with the way the drug effect on you ? ☐ Yes ☐ No

FIGURE 1.
COLLECTION SHEET USED FOR ALL THREE STUDIES

Table 1**Demographic Data**

Variable	N	%
<i>Age</i>		
Mean $\pm$ SD	67 $\pm$ 13	
Median (Range)	69 (30-90)	
<i>Gender</i>		
Male	27	54
Female	23	46
<i>Race</i>		
White	40	80
Black	10	20
<i>Patient Type</i>		
Inpatient	19	38
Outpatient	31	62
<i>Indication</i>		
Depression	40	80
Fatigue	10	20
<i>Primary Diagnosis</i>		
Lung	7	14
Head & Neck	5	10
Breast	5	10
Esophagus	5	10
Pancreas	5	10
Colon	4	8
Multiple Myeloma	2	4
Endometrium	2	4
Prostate	2	4
Sarcoma	2	4
Other *	11	22

* One each of brain, cervix, gastric, Hodgkin's, melanoma, Merkel cell, mesothelioma, ovary, kidney, small bowel, and unknown primary

TABLE 2

Change In Mean Symptom Severity Scores

Symptom	Baseline	Day 3	Day 5	Day 7	P-value
Agitation	0.5±0.7	0.4±0.6	0.3±0.6	0.3±0.6	0.01 *
Anorexia **	0.9±1.0	0.7±0.8	0.7±0.8	0.7±0.8	0.01 *
Dizziness	0.1±0.4	0.1±0.3	0.0±0.3	0.1±0.3	0.01 *
Dry Mouth	0.8±0.9	0.7±0.8	0.8±0.8	0.8±0.8	0.64
Headache	0.0±0.2	0.0±0.1	0.0±0.0	0.0±0.1	0.37
Insomnia	0.4±0.7	0.4±0.7	0.3±0.6	0.3±0.6	0.24
Nausea	0.2±0.4	0.1±0.4	0.2±0.5	0.2±0.4	0.72
Palpitations	0.0±0.1	0.0±0.1	0.0±0.0	0.0±0.0	0.21
Tremors	0.3±0.5	0.2±0.5	0.2±0.5	0.2±0.4	0.15
Vomiting	0.0±0.2	0.0±0.1	0.0±0.1	0.0±0.1	0.48

All Numbers were rounded to one decimal place

* Significant (P<0.05)

** Missing data in one subject

TABLE 3
Published Methylphenidate Prospective Studies In Cancer Patients (N=14; Excluding Case Reports)

Study	N [^]	Final MP Dose (mg/day)	Reported Side effects (S/E)	Withdrawals due to MP Toxicity
Bruera ¹⁰	32	15	Abdominal cramps Diarrhea Drowsiness Headache Insomnia Nervousness Sweating Vertigo *No differences between MP and Placebo but for Nervousness (with MP)	No patient withdrew due to intolerable S/E
Bruera ¹¹	15	42±15	1 patient Agitation and Dysphoria 6 Restlessness 4 Sweating	7% (1 patient) withdrew due to S/E
Bruera ¹²	20	10	No differences between MP and Placebo	1 withdrew due to confusion (suspected to be a terminal confusion syndrome)
Bruera ¹³	31	Up to 20	2 Anorexia 2 Restlessness 1 Dizziness 1 Skin rash 1 Tachycardia 1 Vertigo	No patient on MP withdrew due to intolerable S/E
Bruera ¹⁴	112	11.5 ± 5	Anorexia Behavioral changes Insomnia Restlessness Skin rash Slurred speech Tachycardia Vertigo *No differences between MP and Placebo	No patient on MP withdrew due to intolerable S/E
Butler ¹⁵	68	10-50	Nausea Tachycardia Vomiting *No differences between MP and Placebo	1% (1 patient) withdrew due to increased liver enzymes
Fernandez ¹⁶	30	30-80	Nervousness Palpitations Nausea Confusion Psychosis Constipation Chest pain Tachycardia BP changes	7% (2 patient) withdrew due to MP S/E
Gagnon ¹⁷	14	20-50	Only Nervousness reported	No patient on MP withdrew due to intolerable S/E
Hanna ¹⁸	37	10 - 20	6 patients Restlessness 3 Dizziness 3 Headache 1 Back spasm 1 Palpitation	16% (6 patients) withdrew due to grade 1 S/E
Macleod ¹⁹	26	5-20	Only tachycardia reported	4% (1 patient) withdrew

				due to S/E, another due to unrelated cause
Mar Fan ²⁰	57	10-20	Anxiety Dizziness Insomnia Neurotoxicity (presumed due to MP)	12% (7 patients) withdrew due to S/E
Meyers ²¹	30	20 – 60	Inappropriate behavior Irritability Shaky	7% (2 patients) withdrew due to S/E
Sugawara ²²	21	5-30	Insomnia Palpitation	10% (2 patients) withdrew due to insomnia
Wilwerding ²³	43	10-15	No differences between MP and Placebo groups	21% (9 patients) withdrew. Some due to MP S/E others from other reasons (separate numbers not reported)

S/E = Side effects; MP = Methylphenidate

[^] Numbers of Patients enrolled