Annals of Gastroenterology (2016) **29,** 536-543

Role of methylphenidate in the treatment of fatigue in advanced pancreatic cancer population

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Abstract

Background Fatigue is a common but devastating symptom for advanced pancreatic cancer (APC) patients. To date, no proven treatment exists. Methylphenidate (MPH) showed inconsistent results in treating other cancer related fatigue. We performed a retrospective study to assess MPH in ameliorating fatigue in APC patients.

Methods We retrospectively reviewed our clinic APC patients' records who visited from 06/2011 - 11/2014. Fatigue was assessed by Visual Analog Fatigue Scale (VAFS) and classified as grade 1 (VAFS 1-3), grade 2 (VAFS 4-6) and grade 3 (VAFS 7-10) to correspond with CTCAE V4.0. MPH was dosed at 5 mg daily in the morning and was escalated to 10 mg after 2 weeks if needed. The primary endpoint was to assess the change of fatigue grade after 4 weeks of MPH. Secondary outcomes included MPH's effect on depression, anorexia, maintenance chemotherapy intensity and adverse effects.

Results A total of 71 APC patients on concomitant chemotherapy were included, of whom 67% received doublet, 13% triplet, and 20% single-agent chemotherapy. Mean baseline VAFS was 7, which dropped to 4 after 4 weeks of MPH, 55% patients' fatigue score improved by 1 grade, 8% by 2 grades, 23% had fatigue resolved, 14% without benefit. 72% patients maintained chemotherapy intensity, 39% felt less depression and 52% had improved appetite. 13% stopped MPH due to side effects. Rare Grade 3 or 4 adverse events included insomnia, restlessness, palpitations and anorexia.

Conclusions Our findings support low-dose MPH benefits APC patients with improved fatigue, depression and anorexia. A large randomized clinical trial is needed to confirm its usage and safety.

Keywords Methylphenidate, fatigue, pancreatic cancer, chemotherapy, cachexia

Ann Gastroenterol 2016; 29 (4): 536-543

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Conflict of Interest: None

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Received 21 March 2016; accepted 17 May 2016; published online 16 June 2016

DOI: http://dx.doi.org/10.20524/aog.2016.0065

Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the United States. The majority of patients are diagnosed at advanced or metastatic stage; subsequently, their prognosis is poor with a 5-year survival rate of only 5% [1]. Therefore, much of pancreatic cancer management is focused on symptom control [2]. Cancer-related fatigue (CRF) is the most prevalent symptom in advanced cancer patients [3], especially common and usually severe in advanced pancreatic cancer (APC) patients. It is devastating and significantly influences quality of life, leading to adverse physical, psychosocial, and economic consequences for patients, their caregivers and the whole society [4]. However, it is underreported and underdiagnosed [5] because of the

unawareness of early signs and lack of accurate assessment tools. This devastating symptom is also undertreated because of limited treatment options and it often leads to discontinuation or dose reduction of the anti-cancer treatment. Since fatigue is a very complex syndrome, usually involving multifactorial causes, it is usually attributed to other causes such as anemia or poor nutrient. Fatigue presents as a concomitant symptom of the cancer or as a treatment-associated toxicity secondary to chemotherapy (Table 1), radiation or immunotherapy. It is also associated with significant inter-individual variability; it is often more common and more severe in patients with medical comorbidities, nutritional issues, physical deconditioning, and mood disturbance, it is also influenced by psychosocial and demographic factors. The lack of a thorough understanding of the underlying mechanism of CRF makes it difficult to seek effective treatment.

Several recent studies have shown some positive benefit of methylphenidate (MPH) in treating fatigue in chronic fatigue syndrome [6], HIV [7], prostate cancer [8] and recurrent gynecologic cancers [9]. However, no pharmacological intervention for fatigue has been studied particularly for APC patients. Given the frequency and severity of fatigue in APC patients, and the difficulty to maintain chemotherapy intensity due to the fatigue, it is important to test the potential benefit of MPH in the management of fatigue in this patient population. We performed a retrospective chart review to assess the efficacy of MPH in the treatment of fatigue in APC patients.

Table 1 Frequency of fatigue associated with chemotherapy agent

Chemotherapy agent	% of fatigue associated with agent
Gemcitabine	>30
Irinotecan	>30
Oxaliplatin	>30
5-Fluorouracil	10-29
Capecitabine	>30
Docetaxel	>30
Nab-paclitaxel	<10
Cisplatin	<10

Source: Chemocare.com

Table 2 Grading of fatigue at initiation of methylphenidate by visual analog fatigue scale (VAFS)

	Level (VAFS)	Patient (numbers)	Patient (%)	Patient (numbers)
Grade 2 Moderate	4	6	8	39
	5	4	6	
	6	29	41	
Grade 3 Severe	7	9	13	32
	8	13	18	
	9	7	10	
	10	3	4	
Mean	VAFS 7 at initiation			
Total			100	71

Patients and methods

Patient population

We identified a total of 71 stage 4 pancreatic cancer patients who were experiencing fatigue during the treatment from June 2011 - November 2014 at our outpatient clinic as per our institutional guidelines. Fatigue was reported and documented at each visit based on VAFS (Fig. 1) ranging from 1 to 10 and classified as: Grade 1 or mild (1, 2, 3), Grade 2 or moderate (4, 5, 6) and Grade 3 or severe (7, 8, 9, 10) using the National Cancer Institute Common Toxicity Criteria version 4.03 (Table 2). All patients were on concomitant chemotherapy (Table 3A), and reporting grade 2 or higher fatigue (Table 3B), as defined above, were included.

Response evaluation

Response of fatigue was assessed at each visit prior to the next dose of chemotherapy. To assure the drug effect at equilibrium state [10], a trial of at least 4 weeks of MPH was given before discontinuing the drug due to lack of benefit. Improvement in depressive symptoms and anorexia, in ability to perform activities of daily living (ADLs) and to maintain chemotherapy intensity were also assessed, and documentation was done in our EMR. Q. Do not abbreviate.

Treatment plan

MPH was started at 5 mg PO once daily in the morning with related data from previous studies [11,12] and in consideration of our patient population's age, cardiac risk and cancer-related nervousness. The dose was escalated to 10 mg in patients who did not receive a benefit at the lower dose.

Toxicity assessment/dose modification

A retrospective chart review was done to collect documentation of patient responses. The number of patients who achieved benefit and tolerated MPH was calculated, as well as the number of patients in whom the drug had to be stopped secondary to no benefit or intolerance. The rate of common or significant adverse events was calculated and compared to the rate among general MPH users.

Table 3 (A) Use of chemotherapy in advanced pancreatic cancer patients during methylphenidate treatment

Chemotherapy (%)	Agent	Patient (number)	Patient (%)
Single (20)	Gemcitabine	10	14
	Irinotecan	4	6
Double (63)	Gemcitabine with oxaliplatin	14	20
	Gemcitabine with cisplatin	11	16
	Gemcitabine with nab-paclitaxel *	9	13
	Gemcitabine+ experimental drug**	10	14
Triplet (9)	GTX ***	3	4
	FOLFOX ****	3	4
	Gemcitabine+ nab-paclitaxel+ experimental drug	1	1
Quadruplet (8)	FOLFIRINOX*****	6	8
Total		71	100

*Nab-paclitaxel - albumin bound paclitaxel, **Experimental drug: hedgehog inhibitor, ***GTX- Gemcitabine, docetaxel, and capecitabine, ****FOLFOX- Leucovorin, Fluorouracil, Oxaliplatin, *****FOLFIRINOX- Leucovorin, Fluorouracil, Irinotecan, Oxaliplatin

GTX, Gemzar, Taxatere and Xeloda; FOLFOX, Leucovorin, Fluorouracil, Oxaliplatin; FOLFIRINOX, Leucovorin, Fluorouracil, Irinotecan, Oxaliplatin

Table 3 (B) Baseline (pre-methylphenidate) grades of fatigue in patients receiving different chemotherapy regimens

Chemo regimen	Grade 2 (n)	Grade 3 (n)
Gemcitabine (n=10)	7	3
Irinotecan (n=4)	1	3
Gemcitabine+oxaliplatin (n=14)	7	7
Gemcitabine+cisplatin (n=11)	5	6
Gemcitabine+nab-paclitaxel (n=9)	6	3
Gemcitabine+experimental drug (n=10)	9	1
GTX (n=3)	0	3
FOLFOX (n=3)	3	0
Gemcitabine+nab-paclitaxel+experimental drug (n=1)	1	0
FOLFIRINOX (n=6)	0	6

Gem, gemcitabine; Gem-Ox, gemcitabine with oxaliplatin; Gem-CDDP, gemcitabine with cisplatin; Exp, experimental; GTX, Gemzar, Taxatere, and Xeloda; FOLFOX, Leucovorin, Fluorouracil, Oxaliplatin; FOLFIRINOX, Leucovorin, Fluorouracil, Irinotecan, Oxaliplatin

Statistical analysis

The primary efficacy endpoint was objective improvement in fatigue in the APC population. The response rates by percentage were calculated as shown in Table 4.

Results

Demographics

A total of 71 patients with diagnosed APC who were receiving concomitant chemotherapy were evaluated. The age ranged from 38 to 76 years old; there were 41 males and 30 females. Ten patients were receiving mono-chemotherapy, mainly gemcitabine and irinotecan. A total of 34 patients were on doublet chemotherapy including 14 patients on gemcitabine with oxaliplatin, 11 patients on gemcitabine with cisplatin, and 9 patients on gemcitabine with albumin-bound paclitaxel. Three patients were receiving the triplet regimen GTX (gemcitabine, docetaxel, and capecitabine) or FOLFOX (leucovorin, fluorouracil, and oxaliplatin), while 6 patients were on quadruplet regimen FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin). There were another 11 patients enrolled on a clinical trial, 10 of them on gemcitabine with experimental drug and one patient was on gemcitabine plus albumin-bound paclitaxel and experimental drug (Table 3 A, B).

Dose intensity of treatment

MPH was started at 5 mg PO once daily in the morning and 5/71 (7%) patients were escalated to 10 mg PO with benefit. One patient who had undergone dose escalation required de-escalation back to 5 mg due to insomnia.

Efficacy/response of treatment

The onset of benefit was observed after 2 weeks of treatment with MPH. Benefit was again assessed at 4 weeks to determine the need for dose escalation. Most patients continued MPH (54/71). Among those who continued, duration of therapy ranged from 4 weeks to 24 months. In 39/71 (55%) patients receiving MPH, CRF improved by one grade from grade 3 to grade 2 or grade 2 to grade 1. In 6/71 (9%) patients, CRF significantly improved by two grades from grade 3 to grade 1, and in 16/71 (23%) patients the fatigue resolved (Table 4). Secondary endpoints thought to be associated with MPH in this patient population were also evaluated. Twenty-eight patients (39%) felt less depression, 37 (52%) had improved appetite, 48 (68%) were able to perform ADLs better and 51 (72%) were able to maintain chemotherapy intensity (Table 5).

Safety

Ten (14%) patients stopped the MPH due to lack of benefit after a minimum 4 weeks of use and 9 (13%) stopped due to adverse effects. The most common side effects of MPH in our study were weight loss (6%), nausea (4%), decreased appetite (4%), insomnia (3%), rapid pulse rate (3%), tremor

(1%), nervousness (1%), xerostomia (1%), and anorexia (1%) (Table 6). The extent to which the chemotherapy caused some of these adverse reactions could not be assessed, as well as how much the underlying pancreatic cancer contributed to the common side effect such as weight loss, nausea, decreased appetite, etc.

Discussion

Pancreatic cancer patients are unique population due to the high mortality and rapid progression associated with the disease. Even with the recent medical advancements, the efficacy of existing chemotherapy agents for APC is limited [13]; the 5-year survival rates remain low at 2% [1]. Fatigue has been one of the most common symptoms in APC patients, but there is no proven treatment available at present and a very limited number of studies are available. Our study, one of the largest studies to date, looks at the efficacy of MPH in treating grade 2 or higher fatigue in APC patients receiving concomitant chemotherapy.

Table 4 Methylphenidate effect on fatigue

Time of assessment	Baseline	4 weeks	Patient# (%)
Grade of fatigue	3	3	5 (7)
	3	2	13 (18)
	3	1	6 (8)
	3	0	8 (11)
Grade of fatigue	2	2	5 (7)
	2	1	26 (37)
	2	0	8 (11)
Mean VAFS	7	4	
Overall benefit			
No benefit			10 (14)
1 Grade down			39 (55)
2 Grade down			6 (8)
Resolved*			16 (23)

Grade 1: VAFS Level 1, 2, 3, Grade 2: VAFS Level 4, 5, 6, Grade 3: VAFS Level 7, 8, 9, 10, *All patients with VAFS 0 at 4 weeks assessment are included
VAFS, Visual analog fatigue scale

Table 5 Secondary endpoints of methylphenidate use in advanced pancreatic cancer patients

Other benefits*	Patients (number)	Patients (%)
Less depression	28	39
Improved appetite	37	52
Ability to perform activities of daily living	48	68
Maintenance of chemotherapy intensity	51	72

*Without adding other medications

CRF is the most frequent complain in patients with cancer, with its increased recognition, many studies have been done to look for an accurate measurement and good assessment tools to quantify the degrees of fatigue and to evaluate the efficacy of intervention strategies [14]. Although there is still no universally accepted standard for fatigue measurement, there is a variety of assessment tools developed to assess fatigue and related sequelae. A simple, one-dimensional scale such as the single-item screening tool [15], verbal rating scale (none, mild, moderate, severe) or numeric scale using 0-10 scale, in which mild fatigue is indicated as a score of 1-3, moderate fatigue as 4-6, and severe fatigue as 7-10, are widely used in

Table 6 Grade 3-4 side effects of Methylphenidate use

Side effects	General use [53] (%)	Our study (%)	Discontinued (number)
Central nervous system			
Insomnia	3-12	3	1
Headache	22	0	
Dizziness	7	0	
Tremor	3	1	1
Seizure	Case reports	0	
Blurred vision	2	0	
Stroke/Cerebrovascular accident	Case reports	0	
Psychiatric			
Nervousness including agitation, anxiety and irritability	1-8	1	
Depression	2	0	
Visual hallucinations	Case reports	0	
Cardiovascular			
High blood pressure	<1	0	
Rapid pulse rate, palpitation	3-5	3	2
Gastrointestinal			
Decreased appetite	25	4	1
Xerostomia	14	1	
Nausea	13	4*	
Stomach ache	6-7	0	
Constitutional			
Anorexia	2	1	1
Weight loss	7	6	3
Dermatological			
Dermatoses	5	0	
Miscellaneous			
Infection or viral infection	2	0	
Total			9 (13%)

*Effect of chemotherapy cannot be ruled out

ambulatory oncology practice to monitor symptoms over time. Multidimensional fatigue assessments, like the Piper Fatigue Scale (PFS) [16], the Functional Assessment of Cancer Therapy (FACT) [17], the Cancer Fatigue Scale (CFS) [18], Visual Analog Scale (VAS-F) [19], the Fatigue Symptom Inventory (FSI) [20], and MFSI-SF (Multidimensional Fatigue Symptom Inventory-Short Form) [21], use multiple questionnaires to capture more details including characteristics and manifestations of fatigue, and its impact on function. Most of these tools exhibit good consistency and reliability although with some level of redundancy.

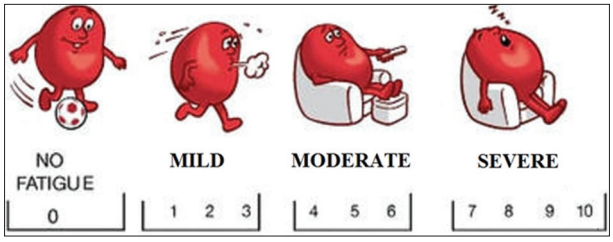
With increased understanding of human genetics, the biological mechanisms of cancer-related fatigue has also been investigated and multiple processes including anemia, cytokine dysregulation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, 5-hydroxytryptophan neurotransmitter dysregulation, and alterations in ATP and muscle metabolism have been identified [22,23]. Inflammation has been recognized as a key mechanism of CRF [24]. Studies show that the pro-inflammatory cytokines, including interleukin (IL)-1β, tumor necrosis factor-α, and IL-6, may be released by the tumor itself or as the result of tissue damage from surgery, radiation, or chemotherapy. These cytokines can send signal to the central nervous system, leading to symptoms of fatigue and other behavioral changes. Alterations in the HPA axis have also been proposed as an underlying mechanism for cancer-related fatigue, either directly or through inflammatory processes [25]. Although the clear mechanism of CRF is still being explored, many studies have been conducted looking at both pharmacological and non-pharmacological interventions for CRF. Currently, there is no gold standard of treatment for CRF. However, variable non-pharmacologic and pharmacologic approaches have shown some benefit [26]. Non-pharmacological interventions include exercise interventions [27], psychosocial interventions [28], mind–body approaches [29], while pharmacological agents include hematopoietic agents such as erythropoietin or darbepoetin for fatigue caused by chemotherapy-induced anemia [30,31], dexamethasone for fatigue in patients with advanced-stage cancer [32], psychostimulants for moderate to severe fatigue in patients with evidence on improvement on quality of life (QoL) and depression [33,34]. Inspired by recent research suggesting the association between the inflammation and CRF, several small trials with anti-inflammatory agents, such as etanercept [35] and infliximab [36,37], have been completed. These have showed some benefit in treating CRF during chemotherapy or in the supportive care setting. Among pharmacologic therapies, the use of MPH shows greater reductions in fatigue as compared to placebo [38] and it has been studied the most among traditional psychostimulants showing possible efficacy with good tolerance despite some common side effects [34,39]. Scarce data is available on modafinil to ameliorate cancer-related fatigue, limited study showed negative benefit for CRF [40]. Also, modafinil required high copayment and has frequent insurance denials [41].

MPH is a central nervous system stimulant, which works by blocking the dopamine transporter and norepinephrine transporter resulting in increased concentrations of dopamine and norepinephrine within the synaptic cleft. It is typically prescribed for attention deficit hypersensitivity disorder [42] but has been recently used, with some success, to treat fatigue in HIV [7] and cancer patients [34]. Psychostimulants, such as MPH and pemoline [43], have been well studied in cancer patients for their additive analgesic effect while decreasing sedation of narcotics [44] and improvement in depression in cancer patients [45] without severe toxicity. Most common side effects of the psychostimulants are insomnia, anxiety, tremulousness, delirium and tachycardia [45]. One case report of MPH use in an APC patient was associated with improvement in mood and psychomotor retardation [46]. Several randomized controlled trials have been conducted to test the role of MPH in ameliorating CRF in other conditions, including prostate cancer [8,47], breast cancer [48], brain tumors [49], after cancer chemotherapy [50] and in general [32,51], but results have been inconsistent [34]. A few meta-analyses have been conducted with numbered studies and concluded limited evidence for the use of MPH to treat CRF [12,33]. One recent phase III randomized, double blind, placebo-controlled study assessed the efficacy of MPH on CRF with target dose at 54 mg/day for 4 weeks [52]. A total of 148 patients with variable cancers, including breast, lung, colon, prostate and others, were randomized to receive MPH or placebo and measured the brief fatigue inventory as the primary outcome. No improvement in the primary endpoint observed with the MPH arm (P=0.35) but a subset analysis suggested some fatigue improvement in patients with severe fatigue and/or with more advanced disease (P=0.02). The most common side effects of MPH were nervousness and appetite loss.

Another phase II randomized, double blind, placebo-controlled trial looked at MPH for fatigue reduction in prostate cancer patients receiving LHRH-agonist therapy [47] Twenty-four men were randomized to receive either 10 mg daily of MPH or placebo. Although the study was closed prematurely due to poor accrual, there was significant improvement in fatigue observed in the MPH arm as compared to placebo after 10 weeks of treatment [+7.7(7.7) vs. +1.4(7.6)]; P=0.022. The within-group analysis also demonstrated a significant improvement in fatigue in the MPH arm (P=0.008) vs the placebo arm (P=0.82) and significantly greater improvement in QoL than placebo (P=0.04).

In our study, all patients with grade 2 or above fatigue were started at 5 mg PO daily of MPH. The majority of patients were able to achieve the benefit at this dose, though a few required higher doses for benefit. MPH significantly reduced the fatigue level, something also associated with chemotherapy (Table 7), alleviated depression and anorexia; these symptoms are common reasons causing APC patients to withdraw or reduce chemotherapy intensity. Our study also shows that MPH helped maintain chemotherapy intensity in APC patients on concomitant chemotherapy. There were no significant side effects and was well tolerated in most of the patients.

In summary, MPH has been shown mixed results in relieving CRF in mixed cancer population. Our retrospective study shows MPH has clear benefit in decreasing the severity of CRF and helping maintenance of chemotherapy intensity



VAFS	1	2	3	4	5	6	7	8	9	10
	Mild			Moderate			Severe			
CTCAE 4.03	Fatigue relieved by rest			Fatigue not relieved by rest, limiting instrumental ADL			Fatigue not relieved by test, limiting self care ADL			

Definition: A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities

Figure 1 Visual analog fatigue Scale (VAFS)
CTCAE 4.03 - June 14, 2010: General disorders and administration site conditions, p56
VAFS, visual analog fatigue scale; *ADL, activities of daily living*

Table 7 Reported fatigue associated with different chemotherapy regimens in pancreatic cancer

Regimen	% Fatigue seen in pivotal trial	Number of patient with fatigue in our study Grade (n)
Gemcitabine [54-56]	Grade 1: 21% Grade 2: 17% Grade 3: 3-18%	G2 (7) G3 (3)
Irinotecan [57]	Grade 1-2: 30%	G2 (1) G3 (3)
Gemcitabine+oxaliplatin [55]	Grade 3: 15% Grade 4: 2%	G2 (7) G3 (7)
Gemcitabine+cisplatin [54]	Grade 1: 12% Grade 2: 23% Grade 3: 5%	G2 (5) G3 (6)
Gemcitabine+nab-paclitaxel [58]	Grade 3: 17%	G2 (6) G3 (3)
Gemcitabine + experimental agent	NA	G2 (9) G3 (1)
GTX [59]	Grade 3-4: 9%	G2 (0) G3 (3)
FOLFOX [60]	Grade 1-2: 76% Grade 3-4: 14%	G2 (3) G3 (0)
Gemcitabine + nab-paclitaxel + experimental drug	NA	G2 (1) G3 (0)
FOLFIRINOX [56]	Grade 3-4: >23.6%	G2 (0) G3 (6)

GTX, gemzar, taxatere, and xeloda; FOLFOX, leucovorin, fluorouracil, oxaliplatin; FOLFIRINOX, leucovorin, fluorouracil, irinotecan, oxaliplatin

in APC patients on concomitant chemotherapy, it was well tolerated at a low but effective dose. Large, placebo-controlled prospective trial assessing the safety and efficacy of MPH are warranted in patients with APC.

Summary Box

What is already known:

- Fatigue is one of the most common symptoms associated with pancreatic cancer
- The pathophysiology underlying the mechanisms of cancer-related fatigue is not adequately understood and may include multiple processes including anemia, cytokine dysregulation, hypothalamic-pituitary-adrenal axis dysregulation, 5-hydroxytryptophan neurotransmitter dysregulation, alterations in ATP, muscle metabolism, and inflammation
- Currently, there is no gold standard of treatment for cancer-related fatigue (CRF)

What the new findings are:

- Our study showed benefit in ameliorating CRF with methylphenidate (MPH) at a low dose of 5 mg in patients with advanced pancreatic cancer with favorable safety profile
- MPH also alleviated depression and anorexia, and helped maintain chemotherapy intensity

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