



Improved cancer-related fatigue in a randomised clinical trial: methylphenidate no better than placebo

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ABSTRACT

Introduction Methylphenidate is a psychostimulant drug used to treat fatigue in patients with advanced cancer, for which there is no gold standard of treatment.

Objective To explore the efficacy of methylphenidate in the relief of fatigue in patients with advanced cancer.

Materials and methods A randomised double-blind placebo-controlled multicentre clinical trial, stratified according to the intensity of fatigue. The treatment was considered effective if the improvement in mean fatigue intensity between baseline values and day 6 was significantly higher in the methylphenidate group than in the placebo group. The responses were measured using the Edmonton Symptoms Assessment System (ESAS) and the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) scales.

Results 35 patients received placebo and 42 patients received methylphenidate. The populations of both groups were homogeneous. Patients receiving methylphenidate did not exhibit statistically significant improvement of fatigue in comparison to patients receiving placebo ($p=0.52$). The mean improvement of fatigue (ESAS) on day 6 was $-1.9 (\pm 2.5)$ in the placebo group, and $-2.3 (\pm 2.6)$ in the methylphenidate group ($p=0.52$). The results obtained with the FACT-F were congruent with those obtained by the ESAS. The responses in patients with severe fatigue were $-2.4 (\pm 2.9)$ in the placebo group and $-3.4 (\pm 2.5)$ in the methylphenidate group; the difference was not statistically significant ($p=0.3$).

Conclusion Methylphenidate was not more efficient than placebo to treat cancer-related fatigue. Fatigue improved significantly after 3 days of treatment and was stabilised on day 6, both with placebo and methylphenidate. The side effects of methylphenidate were mild and infrequent.

Trial registration number EudraCT Registry (2008-002171-27).

INTRODUCTION

Fatigue is a very prevalent symptom exhibited by patients with advanced cancer. It is a multidimensional problem that affects physical, emotional, cognitive, functional, and social aspects and, consequently, the quality of life. Rest causes little relief from fatigue in patients with advanced cancer. Despite the prevalence and clinical relevance, the pathophysiological mechanisms are poorly understood. Some theories suggest inflammatory mechanisms (mediated by cytokines), alterations in the hypothalamic–pituitary–adrenal axis, circadian rhythm, serotonin, ATP or muscle metabolism.¹

There is no standard treatment for cancer-related fatigue.^{2 3} In patients with advanced cancer, the goals of the first assessment are to find potentially treatable causes, such as anaemia, depression, infection, hormonal and metabolic disorders, drug use, or sleep disturbances, and to optimise the control of other symptoms, such as pain, anxiety, depression, dyspnoea and insomnia. Among the available pharmacological options, methylphenidate has been one of the most studied drugs in recent years.⁴

Methylphenidate is a central nervous system stimulant with dopaminergic effects on the basal ganglia, and a double effect (dopaminergic and noradrenergic) on the cerebral cortex. It is indicated for attention deficit disorder in children. It has been used for the relief of depression in patients with advanced diseases, and as



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an enhancer of other antidepressants for major depression.⁵ Side effects observed in clinical trials are scarce and mild. The most common, such as nervousness and insomnia, are more frequently observed at the beginning of treatment, and can be controlled by decreasing the doses.⁶

All in all, the literature supports the existence of a modest benefit obtained with the use of methylphenidate in cancer-related fatigue, with weak evidence. Some studies suggest that patients with more severe fatigue are those who can obtain the greatest benefits from this therapy.⁷

OBJECTIVES

The main goal of the present study was to determine the short-term efficacy of methylphenidate, compared with placebo, in the treatment of moderate and severe fatigue in patients with advanced cancer.

Other goals were: (1) to determine whether the improvement was significantly greater in the subgroup of patients with more intense fatigue; (2) to detect the occurrence of adverse effects related to the treatment; (3) to determine whether the administration of the drug improved the cognitive status of patients with fatigue; (4) to determine whether the improvement in mean fatigue intensity in the subgroup of patients with severe fatigue receiving methylphenidate was greater than in the subgroup of patients with moderate fatigue; (5) to determine the evolution of other symptoms concomitant to fatigue, measured with the Edmonton Symptoms Assessment System (ESAS), in the two groups assessed (ie, methylphenidate and placebo); and (6) to determine whether the improvement in the mean intensity of the sum of the fatigue and depression values was greater in patients with more intense fatigue.

MATERIALS AND METHODS

We conducted a randomised double blind placebo-controlled multicentre phase IIB clinical trial, stratified according to the intensity of fatigue: moderate (Visual Numeric Scale (VNS 5–7) or severe (VNS 8–10). Six Spanish hospitals participated in the study, which was registered in the EudraCT Register (<https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-002171-27/ES>).

Patients

We included patients with a score ≥ 5 according to the VNS for fatigue, aged 18 years and over, diagnosed with advanced cancer, exhibiting cognitive status within normal limits for their age and schooling, with life expectancy of at least 1 month (at the discretion of the physician–researcher), and haemoglobin ≥ 90 g/L. The patients excluded from the study were those with history of hypersensitivity to methylphenidate, glaucoma, hyperthyroidism, liver failure, hypertension or severe heart disease, history of seizures, psychosis,

drug addiction or abuse of psychotropic drugs, suicidal ideation with a structured and feasible plan, severe anxiety, hypercalcemia, hypothyroidism, renal insufficiency, clinical suspicion of infection, and those using drugs that could interact with methylphenidate, such as coumarins, phenobarbital, phenytoin, primidone, phenylbutazone, MAOIs (Monoamine Oxidase Inhibitors) or guanethidine.

Variables

The main variable was the level of fatigue assessed by a VNS included within the ESAS on day 6. The treatment would be considered effective if, in the group receiving methylphenidate, the improvement in mean fatigue intensity, between baseline value and day 6, was significantly greater than the improvement observed in the placebo group. We also measured fatigue using the Functional Assessment of Cancer Therapy–Fatigue (FACT-F). Regarding the cognitive assessment, we used the mini-mental state examination (MM) for screening, and Gagnon’s test for follow-up.

Patient assignment was performed in a stratified manner, based on the severity of fatigue, independently in each group of the study. Treatments with methylphenidate or placebo were assigned to each patient by means of a double-blind, central randomisation process (1:1 ratio). A stratified randomisation list was generated according to the sample size. It determined, prior to the start of recruitment, the treatment that corresponded to each patient number included in the study in each institution, thus allowing a competitive recruitment.

The follow-up period of the patients in the study was six calendar days. The assessments were performed on days 0, 3 and 6. The consultation on day 0 was performed face-to-face focused on the inclusion and exclusion criteria, and completing a clinical history and the baseline data of the ESAS, FACT-F questionnaires and the specific cognitive test. The consultations performed on days 3 and 6, which included the questionnaires and the cognitive test, could be done in person or by telephone. On day 6, we completed the medication records and the specific closing information of the study, which consisted of an assessment of global benefit performed by the treating physician (4-level Likert scale), patients’ decision regarding whether or not to continue treatment for fatigue with the study medication (closed question), and the new prescription in their cases, no longer blind, for the treatment of fatigue. The possible side effects that could occur due to the medication under study were assessed in each visit.

Masking

The treatment of the study was prepared so that neither the researcher nor the patients were aware of the assigned treatments. To that end, the placebo group received tablets manufactured without the active

substance, but with the same external appearance as the tablets manufactured with methylphenidate.

Dosage

The initial dose of methylphenidate was 10 mg at breakfast and 5 mg at the other meals, administered in 5 mg tablets. Daily doses were adjusted in successive reviews between 10 and 25 mg/day of methylphenidate at the discretion of the attending physicians. The participation in the study did not interfere or modify the medication that each patient was receiving at the beginning of the study, or the medication that could be required during the trial. Treatment compliance was estimated by assessing the used blisters and the remaining medication.

Assessment questionnaires

Edmonton Symptoms Assessment System

This scale includes several VNSs (with a score of 0–10), and the patients should indicate the severity of frequent symptoms exhibited by patients with advanced cancer. The VNS for fatigue included in the ESAS has a sensitivity of 0.74 and a specificity of 0.63 to detect fatigue considering a cut-off value of ≥ 4 .⁸

Functional Assessment of Cancer Therapy-Fatigue

This subscale is composed of 13 items and assesses fatigue and its impact on activities of daily living. The score of each item ranges between 0 and 4. The total value ranges between 0 (the worst fatigue) and 52 (the mildest fatigue). Patients with fatigue are considered those with a score ≤ 34 .

Cognitive test (Gagnon Test)

We assessed specific changes in spatial vision, attention, and memory applying a questionnaire specifically prepared for the present study, including items of three validated instruments, namely: MM; 3MS (modified MM); and Repeatable Battery for the Assessment of Neuropsychological Status. The reduction of items was intended to facilitate the cognitive assessment of patients with moderate/severe fatigue, including seven sections: (1) repetition of five-word lists; (2) repetition of numerical listings forward; (3) repetition of numerical listings backwards; (4) repetition of the word lists of the initial test; (5) drawing the intersection of two pentagons; (6) writing a dictated phrase; and (7) repetition of the word listings.

Statistical analysis

The present study was designed to detect differences between effects of methylphenidate and placebo in the fatigue level of 1.5 points according to the VNS, between baseline value and day 6. According to data from a study conducted with patients with severe fatigue, the estimated SD of the average relief with methylphenidate was 2.6.^{9–11} The sample, estimated with alpha level of 0.05 and power of 80%, included

98 patients (49 in each group). If a 20% loss was added, 118 patients would be required for the sample.

We performed a descriptive analysis of the demographic data and baseline and follow-up measurements of the patients, using the mean and SD, or median and 25th and 75th percentiles for quantitative variables, and percentages for qualitative variables. Normality was assessed using Kolmogorov-Smirnov test. The trial protocol included an analysis of the results by intention-to-treat and another by protocol. The level of statistical significance was set at 0.05. Statistical analyses were performed with the Stata V.14 software (StataCorp 2015. Stata Statistical Software: Release 14. StataCorp LP).

RESULTS

From January 2011 to March 2016, 100 participants were included in the trial, 55 in the methylphenidate group and 45 in the placebo group. The characteristics of these patients are illustrated in [table 1](#). The trial finished before obtaining the expected number of patients due to slow recruitment. The study was completed by 77 patients (77%), 43 in the methylphenidate group and 34 in the placebo group ([figure 1](#)). The statistical power of the study to detect a relevant minimum difference of 1.5 and an SD of 2.6 was 70.1%, taking into account a two-tailed significance level of 0.05.

In the study population, 47% of the participants were women and 53% men, and the average age was 66.4 years. More than half of the patients had tumours of gastrointestinal origin, almost 20% gynaecological and 17% pulmonary. The life expectancy estimated by the researchers was less than 3 months for half of the patients, and less than 1 year for the others. Only 5% of the participants were estimated to have a survival greater than 1 year. Regarding functional status, most could take care of themselves with occasional help. The cognitive states of the participants were good, with an average of 28.5 points over a maximum of 30 in MM. Almost all symptoms had a value of less than 4 out of 10, which we considered a good control. Depression was around 4/10, and appetite around 5/10. The mean fatigue was 7.3/10 in the two groups.

We also carried out a comparative study of the demographic and clinical variables, between the population of patients who abandoned the study before day 6 and the patients who completed the study. There were no differences between the two groups.

On day six, 67% of patients maintained the initial dose of methylphenidate (15 mg/day).

Effectiveness

Methylphenidate was not more effective than placebo in the study population ([table 2](#)). The reduction in the fatigue score (VNS) was found on day 6 in the two groups. The intensity decreased an average of 2.3 (from 7.3 to 5.0; $p < 0.001$) in the methylphenidate group,

Table 1 Demographic and clinical baseline characteristics of patients

	Placebo n=45	Methylphenidate n=55	Total n=100	P value
Sex (n; %)				
Female	21 (46)	26 (47)	47 (47)	0.95
Male	24 (53)	29 (52)	53 (53)	
Age (years) (mean; range)	68 (39–88)	66 (38–87)	67 (38–88)	0.64
Life expectancy (months; %)				
From 1 to 3	21 (47)	25 (45)	46 (46)	0.95
From 4 to 12	21 (47)	24 (44)	45 (45)	
From 13 to 24	1 (2)	3 (5)	4 (4)	
More than 24	0 (0)	1 (1.8)	1 (1)	
Unknown	2 (4)	2 (4)	4 (4)	
Extension of the disease (n; %)				
Local	5 (11.1)	4 (7.3)	9 (9)	0.91
Locoregional	3 (6.7)	3 (5.5)	6 (6)	
Metastasis	37 (82.2)	47 (85.5)	84 (84)	
Lost	0 (0)	1 (1.8)	1 (1)	
Karnofsky index (mean; range)	70 (40–90)	60 (30–80)	60 (30–90)	0.32
Mini-mental examination (average score; SD)	28.4 (1.6)	28.5 (2.5)	28.5 (2.1)	0.28
Blood pressure, mm Hg, (mean; SD)				
Systolic	118 (18)	117 (15)	117 (16)	0.89
Diastolic	71 (11)	72 (11)	71 (11)	0.65
Heart rate (mean; SD)	83 (14)	83 (14)	83 (14)	0.86
Haemoglobin (g/L) (mean; SD)	116 (18)	111 (22)	113 (21)	0.17
ESAS symptoms* (mean; SD)				
Pain	2.5 (2.6)	2.1 (2.1)	2.3 (2.3)	0.75
Fatigue	7.2 (1.5)	7.4 (1.7)	7.3 (1.6)	0.65
Drowsiness	3.4 (2.8)	4.1 (3.2)	3.8 (3)	0.30
Nausea	1.1 (2.1)	1.6 (2.6)	1.4 (2.4)	0.44
Appetite	5.1 (3.7)	5.3 (3.4)	5.2 (3.5)	0.90
Dyspnoea	1.9 (2.9)	1.5 (2.4)	1.7 (2.6)	0.70
Depression	4.6 (3.4)	4.2 (3.1)	4.4 (3.2)	0.07
Nervousness	3 (3.3)	2.3 (2.7)	2.6 (3)	0.65
Insomnia	3.8 (3.2)	2.6 (3)	3.1 (3.1)	0.07
Wellness	6 (2.6)	4.7 (2.4)	5.2 (2.6)	0.04
Fatigue—FACT-F (mean; SD)*	23.2 (8.4)	22.5 (8)	22.8 (8.2)	0.69

Complete data of days 0, 3 and 6.

ESAS, Edmonton Symptoms Assessment System; FACT-F, Functional Assessment of Cancer Therapy-Fatigue.

and 1.9 (7.3 to 5.4; $p < 0.001$) in the placebo group. No significant differences were found in the reduction between the two groups of the study ($p = 0.52$). The reduction in fatigue levels was evident in the intermediate assessment performed on day 3, and tended to remain similar in the assessment of day 6 (figure 2).

Patients with more intense fatigue receiving methylphenidate did not improve more than the patients who were receiving placebo (figure 3). In patients with moderate fatigue, the intensity decreased an average of

1.2 (from 5.9 to 4.7; $p = 0.02$) with methylphenidate and 1.4 (from 6.3 to 4.9; $p = 0.01$) with placebo. No differences were found in the reduction between the two groups ($p = 0.84$). Regarding patients with severe fatigue, the intensity was reduced by an average of 3.4 (from 8.8 to 5.4; $p < 0.001$) with methylphenidate and 2.5 (from 8.5 to 6.0; $p = 0.05$) with placebo.

We did not find differences in the reduction of fatigue between the methylphenidate and the placebo groups ($p = 0.37$). Also, there were no differences between the

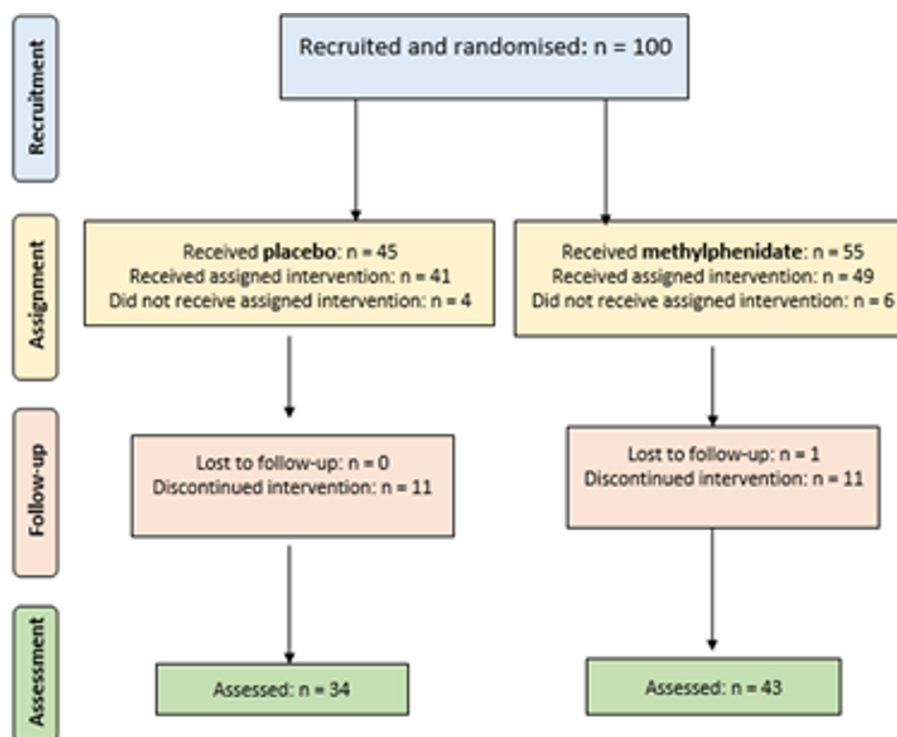


Figure 1 Flow diagram of progress through the phases of the trial (Consolidated Standards of Reporting Trials).

two groups of the study regarding the evolution of the other symptoms included in the ESAS. The results obtained with the FACT-F are congruent with those obtained by the ESAS (table 3).

Almost all symptoms improved on day 6, both in the placebo group and in the methylphenidate group. Pain worsened in the placebo group, and insomnia in the methylphenidate group. None of the changes were statistically significant. In patients with severe fatigue, the improvement in the mean intensity of the sum of fatigue and depression values, between baseline value and day 6, was not greater in patients receiving methylphenidate than in those receiving placebo (table 4).

The number of patients whom completed all cognitive test by day 6 was 74, 31 from placebo arm, and 43 from methylphenidate. No significant differences were found between the methylphenidate and the placebo groups in the results of any of the seven tests included in the cognitive test. Differences were also not found when the outcomes of patients with moderate fatigue

and patients with severe fatigue were assessed separately (table 5).

Safety

Some adverse effects were observed in 27 (49%) patients receiving methylphenidate, and in 17 (38%) patients receiving placebo. There was a higher incidence of nausea, sleep disturbance and nervousness in the methylphenidate group. They were mostly mild side effects that were not related to the treatment. There were six serious adverse effects; two of them had received placebo and four had received methylphenidate; however, none of the cases was considered to be related to the trial.

DISCUSSION

Methylphenidate was no more effective than placebo in improving cancer-related fatigue. However, the fatigue of the patients indisputably improved during the trial, a fact that was evident from the first measurement we performed on day 3. Patients in the placebo group improved equally as those in the methylphenidate group. They improved not only in terms of intensity (ESAS), but in the impact on their daily lives (FACT-F). It was surprising to observe how, in a double-blind intervention, we could find such similar results between the placebo group and that receiving the theoretically active drug. A recent systematic review and meta-analysis suggest that the placebo response in trials testing drugs for cancer related fatigue is non-trivial and should be considered. Nevertheless, no

Table 2 Response assessment: mean improvement in fatigue (ESAS) on day 6

	Placebo n=34	Methylphenidate n=43	P value
Mean	−1.9	−2.3	0.5
SD	(2.5)	(2.6)	
P value	<0.001	<0.001	
*ESAS (Edmonton Symptoms Assessment System) 10/10: the most intense fatigue.			

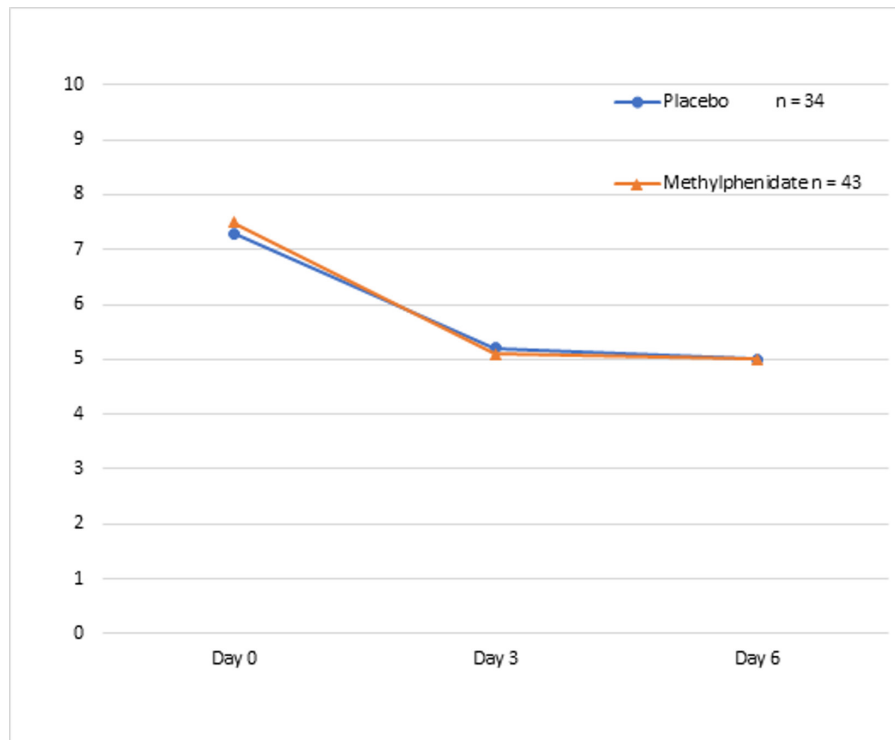


Figure 2 Evolution of mean fatigue (mean; ESAS). ESAS, Edmonton Symptoms Assessment System. ESAS 10/10: the most intense fatigue.

factors related to placebo response were identified in a meta regression.¹²

Looking at the history of research on methylphenidate in oncology and palliative care, it is clear that the recruitment of patients is a very complex issue. Many studies obtain small sample sizes or with little statistical power. The final sample tripled the average size

found in trials with similar characteristics published in the last 6 years.¹³ However, we assume as a limitation that recruitment difficulties certainly involve a loss of power. When we look for data in patients with cancer receiving palliative care, we find very diverse populations composed of patients with cancer and patients with non-cancer at the same time and at different

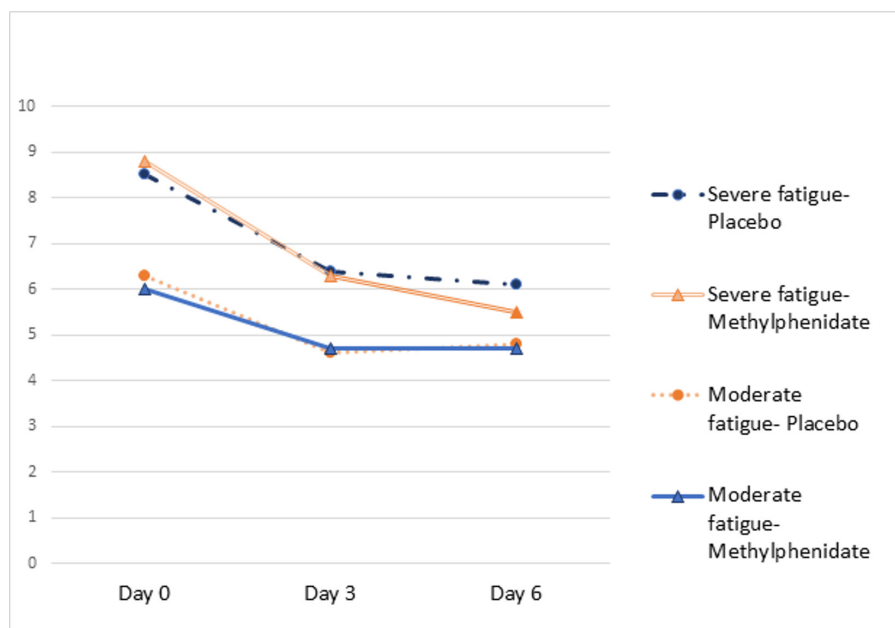


Figure 3 Evolution of fatigue according to initial intensity (mean; ESAS). Severe fatigue—placebo: n=14. Severe fatigue—methylphenidate: n=21. Moderate fatigue—placebo: n=19. Moderate fatigue—methylphenidate: n=23. ESAS, Edmonton Symptoms Assessment System. ESAS 10/10: the most intense fatigue.

Table 3 Response assessment: mean improvement in fatigue (FACT-F) on day 6

	Placebo n=30	Methylphenidate n=43	P value
Median	+6.4	+4.9	0.43
95% CI	3.3 to 9.4	1.6 to 8.2	
P value	0.0002	0.0004	
There are no differences between placebo and methylphenidate.			
*FACT-F 0/52: the worst fatigue.			
FACT-F, Functional Assessment of Cancer Therapy-Fatigue.			

stages of the disease. However, in the present study, the population finally recruited was homogeneous including only patients with advanced cancer (the estimated survival rate for 95% of patients was less than 1 year). In this sense, the present study provides a sample of patients with cancer with different tumours, in comparison to other studies that include patients who are mostly diagnosed with the same diseases, breast or prostate cancer, for example.

The duration of our trial seems adequate. The response was observed from day 3, and was maintained on day 6. It has been described that the efficacy of methylphenidate is rapid.¹⁴ A meta-analysis conducted with subgroups indicated that the response was also maintained over time when treatments were prolonged.¹⁵ We used a dose that seemed to be sufficient to achieve effects, and superior to that of other trials, without finding notable adverse effects. We used simple (ESAS) and impact (FACT-F) scales, and the results obtained with the two scales were similar.

Our trial was stratified by fatigue intensity. The response of severe fatigue to methylphenidate was greater than the response to placebo, with a difference of one point. Although this difference does not reach statistical relevance, it can have some clinical significance. One of the possible factors that may have influenced the results was the tendency of regression to the mean, that is, if a variable is extreme in its first measurement, it will tend to be closer to the mean in its second measurement.¹⁶ The responses could depend on individual factors, such as the previous level of activity, concomitant symptoms or the age of the patients. Previous studies have suggested the relationship of fatigue, and its response to symptomatic treatment, with other symptoms.¹⁷ Our results did

Table 4 Response assessment: improvement of fatigue plus depression (ESAS) on day 6 depending on the initial value of fatigue

Initial value of fatigue	Placebo			Methylphenidate			P value
	n	Mean	SD	n	Mean	SD	
Moderate	19	-2.42	(3.4)	23	-2	(4.2)	0.9
Severe	14	-3.2	(5.4)	19	-5	(5.3)	0.3
*Fatigue ESAS (5–10/10)+depression (0–10/10).							
ESAS, Edmonton Symptoms Assessment System.							

not indicate differences in the evolution of symptoms, measured with the ESAS, comparing methylphenidate and placebo. In our study, almost all symptoms had improved on day 6. The patients were subjected to the same symptom control plan used in the usual activities of the palliative care teams that provided care to them, given that this was a double-blind trial. It has also been suggested that symptomatic treatment for fatigue is most effective when other symptoms such as depression and drowsiness are present.^{7 18} In our study, in patients with severe fatigue, the improvement in the mean intensity of the sum of the values of fatigue and depression, between baseline values and day 6, was not greater in patients receiving methylphenidate. Future research should focus on identifying which subgroups of patients can best respond to psychostimulants.

Methylphenidate did not improve cognition according to the results of our study. One of the inclusion criteria was scoring an MM within the expected values for the age and education of the patients. This criterion made it possible that they could complete the necessary scales, but it is likely that our study was biased due to the fact that we recruited patients with a more physical and less central fatigue. It is also possible that we did not observe effects on cognition because, on average, the sample had a very good cognitive status (see demographic table) and there was little to improve.


Palliative care is a complex intervention, not only based on treating with drugs, but on an integral intervention. In the same way, some research biases are sometimes attributed to the placebo effects, for example, the act of participating in a clinical trial can produce an improvement of the symptoms due to the observations that the patient receives from the researchers (Hawthorne effect).

The patient–physician relationship plays a fundamental role. In this case, the physicians were also the researchers who proposed the trial. The beliefs and expectations of the patients regarding the physicians may affect their behaviours in such a way that they could tend to confirm the doctor's beliefs and expectations. A very close relationship is generated between the researchers and the subjects of a study. There is a great commitment on the part of the patients with the outcomes that are expected from them (Pygmalion effect).

Several problems should be solved in order to improve the management of patients with cancer-related fatigue.¹⁹ The first step would be conducting basic research, in order to know and better understand the pathophysiology and the factors that influence the sensation of fatigue. We should better determine which characteristics of patients' fatigue can help us choose the best individualised treatments.

There is little evidence and there are no strong recommendations for the symptomatic management of cancer-related fatigue. However, as evidenced by

Table 5 Changes in cognitive function (Gagnon cognitive test) at day 6, according to initial fatigue level†

		Moderate fatigue Mean (SD)		Severe fatigue Mean (SD)	
Questions (Q)	Rank	Placebo	Methylphenidate	Placebo	Methylphenidate
Repeating a list of words					
Immediate repetition (Q1)	(0–5)	–0.4 (0.6)	0.0 (0.9)	–0.3 (0.7)	–0.2 (1.0)
Deferred repeat 1 (Q4) *	(0–5)	+0.3 (1.9)	0.0 (2.1)	+0.5 (2.3)	0.6 (1.4)
Deferred repeat 2 (Q4)* (Q7)†	(0–5)	+0.4 (1.8)	0.2 (2.1)	+0.3 (1.7)	0.4 (1.6)
Repeating progressive series of digits					
Forward (Q2)	(0–84)	+2.2 (17.5)	6.3 (17.6)	+1.5 (8.5)	1.9 (16.9)
Backward (Q3)	(0–70)	–0.3 (7.3)	0.5 (9.1)	–0.1 (6.0)	2.0 (10.0)
 Accuracy when copying figure (Q5)	(0–10)	0.0 (1.5)	0.0 (2.4)	–0.2 (2.0)	–0.1 (2.1)
Write a given phrase (Q6)	(0–4)	+0.1 (0.4)	0.3 (0.7)	–0.8 (1.9)	0.4 (0.7)
*Alternating questions 2 and 3.					
†Alternating questions 5 and 6.					
#No comparison between placebo and methylphenidate is statistically significant.					

*Alternating questions 2 and 3.

†Alternating questions 5 and 6.

‡No comparison between placebo and methylphenidate is statistically significant.

different publications and essays, it is clear that there are several groups working in this field. In order to enhance the number of studies and generate more evidence, it is necessary to design clinical trials with a consensus on tools for screening and monitoring fatigue, doses of drugs used, and homogeneity of the populations studied. In addition, it is essential to encourage collaborative research to join efforts.

We have to be creative in dealing with challenges—such as the placebo effect or the difficulty of recruitment—to conduct clinical trials assessing patients with advanced diseases.²⁰ For example, we should investigate how to take advantage of the placebo effect to design therapeutic strategies that relieve our patients, without exposing them to side effects caused by ineffective drugs, or systematically measure the expectations of recruited patients.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The protocol was approved by the Research Ethics Committees of the institutions in which the trial was conducted. The institutional review board at each of the participating institutions approved the study. All patients signed an informed consent form before being included in the clinical trial.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs

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