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Role of methylphenidate in cancer-related fatigue: A Systemic Review

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ABSTRACT

Introduction: Cancer-related fatigue (CRF) is a substantial medical issue that affects patients at all phases of their therapy and escalates with advanced cancer. To gather indications for the use of methylphenidate is objective of the study for the treatment of CRF, as well as to analyse the efficiency and safety of methylphenidate for the treatment of CRF so that we can tailor methylphenidate treatment to response patient only.

Methods: To conduct the review of RCTs Systematic Reviews (PRISMA) statement was ideally chosen for Reporting Items. From inception through the first week of October 2021, A systematic search of the electronic databases PubMed, Embase, PSYCHInfo, and the Cochrane Library was done without any language restrictions. This helped to find all RCTs about the use of methylphenidate in patients with CRF. Search terms used were: methylphenidate, dexmethylphenidate, Ritalin, cancer, tumor, carcinoma, neoplasm, fatigue, asthenia, tiredness, CRF, and RCT. We also looked over a few journals' references to find more theoretically related papers.

Results: A total of 267 citations were screened; among them, after a preliminary review 231 were excluded. 36 full-text articles assessed for eligibility; among them, 10 articles were met the inclusion criteria where all the selected articles were of good quality. Among 10 studies, 5 were identified in mixed tumor, 2 in prostate cancer, 1 in GI cancer, 1 in advanced cancer and 1 in Gynaecologic cancer. The characteristics of the studies changed broadly in terms of the treatment term and the population studied.

Conclusion: To summarize up this study, cancer-related weakness could be critical clinical issue for cancer patients. Our findings suggest that methylphenidate may be useful in the treatment of CRF, but the evidence is inconclusive and has to be confirmed in a bigger study. All of the investigations, however, had tiny sample sizes. This counsel must be respected as provisional and temporary within the absence of considerable information from a single, expansive, well conducted randomized controlled trial. To support and propose new research topics and interventions, more study into biological factors affecting weariness is required.

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INTRODUCTION

Cancer-related fatigue (CRF) is a significant medical condition that affects patients throughout their treatment and worsens with advanced cancer. 1 CRF is defined as "a painful persistent, subjective sensation of weariness or exhaustion linked with cancer or cancer treatment that is not proportional to recent activity and interferes with regular functioning," according to the National Comprehensive Cancer Network (NCCN). 2 The severity and persistence of CRF, as well as the inability to relieve it through rest or sleep, set it apart from other types of exhaustion. It is debilitating and has a significant influence on quality of life, with negative physical, emotional, and financial consequences for patients, caregivers, and society at large.[3] CRF affects over 65% of cancer patients; more than two-thirds of these patients had severe CRF for at least six months, and a third had persistent fatigue for years following treatment. 4-6 Depending on the type of treatment and the type and stage of cancer, the number of patients who acquire CRF varies between studies, ranging from 25% to 100%. 7-10 Up to 40% of patients report fatigue at the time of their cancer diagnosis, and 80 percent to 90 percent report fatigue during chemotherapy (CT) and/or radiotherapy (RT), with 17 percent to 21 percent reporting fatigue during ChT alone and 33 percent to 53 percent reporting fatigue during the combination of ChT and RT.[4,11]

Methylphenidate has been used to treat children with attention deficit hyperactivity disorder (ADHD) since the 1950s (ADHD). MPH is a psychostimulant that works by increasing dopamine levels in the central nervous system, making it a preferred first-line treatment for attention deficit hyperactivity disorder (ADHD).[12-14] Methylphenidate has been used beyond the scope of its license for a variety of indications in patients with advanced conditions, including opioid-induced drowsiness, depression treatment, and fatigue management.[15-17] Methylphenidate is often used twice a day, at breakfast and lunch, to alleviate insomnia. Peak plasma concentration occurs between 1 to 3 hours, with an average half-life of 2 hours. The clinical action time of sustained-release formulations is 4 to 6 hours. Newer sustained-release formulations have an early onset and last for up to 8 hours. It's crucial to keep a look out for common side effects including agitation and insomnia, especially during the first few days of treatment.[18]

The mechanism of action works to extend the levels of this neurotransmitter within the central nervous system (CNS).[19] This is accomplished by restricting dopamine uptake back into the cell and blocking dopamine breakdown in the synaptic cleft, as well as promoting neurotransmitter synthesis. All of these processes work together to increase the quantity of dopamine that can bind to active receptors.[20] To date, the usage of psychostimulants has been limited due to these nonspecific methods of action. In recent experience, this has meant that these medications have no other approved indications for use besides attention deficit disorder.[21] Based on available evidence, methylphenidate appears to have pharmacokinetic features that limit its potential for abuse when compared to other stimulant drugs of abuse, such as cocaine.[22] Several previous trials have shown that it is a viable treatment that is well tolerated in people with various types of cancer.[23,24] The evidence for methylphenidate's efficacy in the treatment of CRF is, however, limited, and it is mostly inferred from randomized studies in other diseases or side effects, or based on non-randomized trials. For example, Johnson et al. and Gehring et al. both supported the use of methylphenidate to treat fatigue, despite a number of disadvantages such as a small number of patients, a short follow-up period, an open-label protocol, and the lack of a placebo.[25-246]

The objective of this study is to gather more evidence for the use of methylphenidate in the treatment of CRF, as well as to analyze the efficacy and safety of methylphenidate in the treatment of CRF so that we can tailor methylphenidate treatment to those patients who react to it.

METHODS

The RCTs were reviewed using the Preferred Reporting Items for Systematic Reviews (PRISMA) statement. A comprehensive search of the following electronic databases, PubMed, Embase, PsycINFO, and the Cochrane Library, was done from their establishment through the first week of October 2021, and identified all RCTs linked to the role of methylphenidate in patients with CRF. The following keywords were used in our search: "methylphenidate", "dexmethylphenidate", "dMPH", "ritalin", "cancer", "tumor", "carcinoma", "neoplasms", "fatigue", "asthenia", "tiredness" In addition, we manually reviewed the references of a few journals to uncover more works that might be linked. A comprehensive set of search terms, as well as a systematic review methodology, were used. These procedures are described in more detail elsewhere.[26] In summary, one author examined relevant titles and abstracts before retrieving full-text publications if needed. The final list of research to be included was agreed upon by all of the authors. Only randomized controlled trials in the treatment of CRF that compared the use of a psychostimulant to placebo or usual care were included. When raw data acceptable for inclusion in a systemic review was required, the authors were contacted.

Inclusion criteria

Original studies were considered for inclusion in the meta-analysis if they met the following criteria: they were randomized controlled trials (RCTs); patients over the age of 18 with cancers like Breast, Prostate, Lung, Genitourinary, Gastrointestinal, Hematologic, and Brain tumors were investigated. The effectiveness of methylphenidate on fatigue was investigated, and the results were sufficient to compute impact sizes.

Data extraction and Statistical analysis

Two clinicians separately examined the total papers of qualified trials. The name of the primary author, the year of publication, the sample size, patient characteristics (mean age, gender), cancer type, therapy dosage, treatment duration, outcomes, study design, and country were all extracted. Using predesigned data extraction forms, data were extracted and independently reviewed. The information was entered into the Cochrane review manager program.[27]

Prisma flow chart

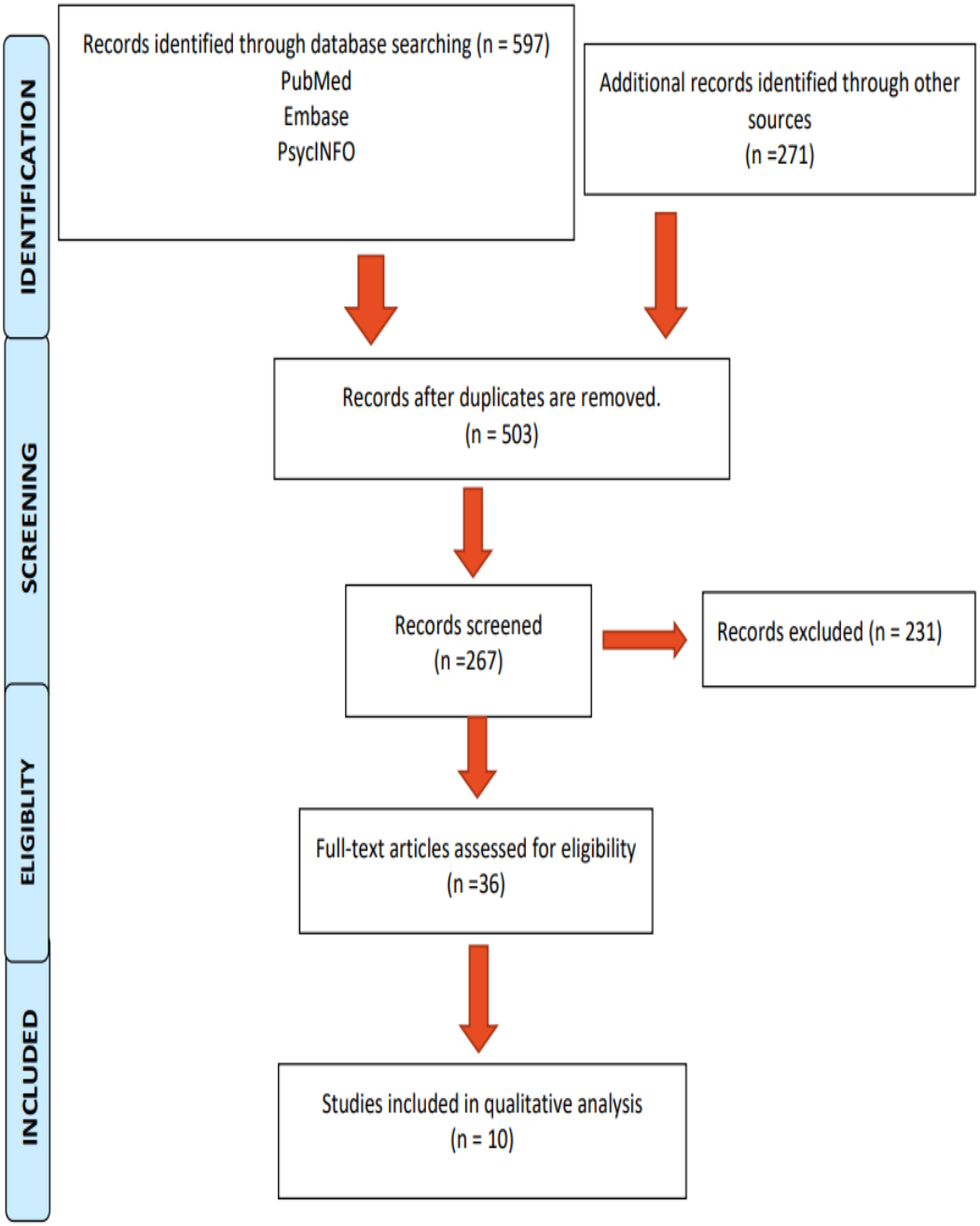

Figure 1: The selection mechanism schedule of records relevant to the present study in accordance with the PRISMA technique

RESULTS

The Preferred Reporting Items for Systematic Reviews (PRISMA) statement was used to conduct the review of RCTs (Figure 1). All RCTs linked to the use of methylphenidate in patients with CRF were identified using a total of 597 citations from the electronic databases PubMed, Embase, PsycINFO, and the Cochrane Library, which were searched without language restrictions from their inception. The following keywords were used in our search: "methylphenidate", "dexmethylphenidate", "dMPH", "ritalin", "cancer", "tumor", "carcinoma", "neoplasms", "fatigue", "asthenia", "tiredness". In addition, we manually searched the references of a few journals to find more potentially relevant studies. Due to redundancy, 94 citations were eliminated from the total of 597. A total of 267 citations were reviewed, with 231 of them being eliminated following a preliminary review. Thirty-six full-text publications were evaluated for inclusion. There were ten papers that satisfied the inclusion criteria, and all of the articles that were chosen were of high quality (Figure 1). Five studies were found in mixed tumors, two in prostate cancer, one in gastrointestinal cancer, one in advanced cancer, and one in gynecologic cancer (Table 1). In terms of treatment length and population investigated, the studies had a wide range of features. These details are summarized in Table 1

Table 1: Summary of randomized controlled trials on the role of methylphenidate in cancer-related fatigue.

S N.	Author	No. of Participants	Study Design	Type of cancer	Intervention	Primary Outcome	Questionnaire used	Comments
1	Bruera et al.[28]	141	Randomized, 4-arm, placebo-controlled	GI cancers	Methylphenidate 5–20 mg/day + nurse telephone intervention OR control telephone intervention for 15 days	Effect on fatigue after 15 days	FACIT-F	All groups showed a significant effect in improved fatigue on day 15. MPH was not superior to placebo from baseline to end of the trial (5.5 vs. 6.0, p = 0.69).
2	Pedersen et al.[29] 2020	38	Randomized, double-blind, placebo-controlled	Advanced cancer	10 tablets of Methylphenidate 10 mg and 10 tablets placebo, randomly packed	Effect on fatigue after 2 and 5 h.	VAS tiredness	Significant effect with MPH but not placebo after 2 h (mean difference in decrease -12, SD 20, p = 0.004) and after 5 h (mean difference in decrease -12, SD 19, p = 0.001)
3	Mitchell et al.[30] 2015	43	Randomized, N-of-1, double-blind, placebo-controlled crossover, multicycle design	Mixed tumor	Methylphenidate 5 mg × 2 for 3 days, placebo for 3 days, methylphenidate 5 mg × 2 for 3 days. 3 cycles.	Effect on fatigue as individual comparison + population estimate	FACIT-F	No difference was detected between groups characterized as responders and non-responders after 84 completed cycles, mean difference 3.2 (95% credible interval −2.0, 9.0). 7 patients had the clinically significant positive effect of MPH.
4	Centeno et al.[31] 2020	100	Randomized, double-blind, placebo-controlled	Mixed tumor	Methylphenidate 10–25 mg/day for 6 days	Effect on fatigue after 6 days.	ESAS, FACT-F	No significant difference between treatment arms (ESAS p = 0.52, FACT-F p = 0.3). Mean improvement in MPH group: ESAS −2.3 (SD 2.6), FACT-F −3.4 (SD 2.5) Placebo group: ESAS −1.9 (SD 2.5), FACT-F −2.4 (SD 2.9)
5	Richard et al.[32] 2015	24	Randomized, double-blind, placebo-controlled	Prostate cancer.	Methylphenidate 5–10 mg/day for 12 weeks	Effect on fatigue after 10 weeks	FACT-F	After 10 weeks mean difference in change from baseline was 5.6 points in favor of the intervention (95% CI 1.0–10.3), p = 0.022.
6	Roth et al.[33] 2010	32	Randomized, double-blind, placebo-controlled	Prostate cancer.	Methylphenidate 5–30 mg for 6 weeks. Individual titration of dose after day 3.	Effect on fatigue after 6 weeks.	BFI	Significant effect of both MPH and placebo (improvement in BFI total score 3.63, p = 0.01 and 2.58, p = 0.02), comparison between groups not shown. Methylphenidate reduced BFI severity score more than placebo (p = 0.03). RR for fatigue improvement in the MPH group was 3.04 (CI 1.04–8.86) compared to placebo (p = 0.02)

7	Johnson et al.[34] 2009	32	Open-label, prospective	Gynecologic cancer	Methylphenidate, 5 mg, twice daily for 8 week	Effect on fatigue after 8weeks.	FSI	Patients reported a significant decline in fatigue (P = .0001) as measured by the Fatigue Symptom Inventory Improvement in mood and quality of life were also observed
8	Moraska et al.[35] 2010	148	Randomized, double blind, placebo controlled	Mixed tumor	Methylphenidate (target dose, 54 mg/d) or placebo for 4 weeks.	Effect on fatigue after 4weeks	BFI, AUC	Long-acting methylphenidate product would decrease cancer-related fatigue. improvement in usual fatigue was 19.7 with methylphenidate v 2.1 with placebo; P =.02)
9	Lower et al.[36] 2009	154	Randomized, double blind, placebo controlled	Mixed tumor	Methylphenidate, 5 mg, twice a day for 1 week	Effect on fatigue after 8 weeks	FACIT-F	Compared with placebo, methylphenidate-treated subjects showed a significant improvement in fatigue symptoms in the FACIT-F at eight weeks.
10	Escalante et al.[37] 2014		Randomized, placebo controlled, crossover	Mixed tumor	Methylphenidate 18 mg/day for 14 days + placebo for 14 days.	Effect on fatigue assessed as improvement of worst level of fatigue after 14 days.	BFI	No significant difference between treatment groups (p = 0.54) regarding the worst level of fatigue after 14 days of treatment.

DISCUSSION

This is the first systematic review that we are aware of that quantifies the role of methylphenidate in cancer-related fatigue. Since our original systematic review, more evidence about the use of methylphenidate to treat CRF has emerged.[26]

Despite a number of early studies showing the efficacy of methylphenidate therapy for cancer-related fatigue management, the results of this study indicated no statistically significant benefit for 54 mg/d long-acting methylphenidate doses compared to placebo for cancer-related tiredness relief. When comparing the two treatment arms, secondary endpoints such cancer-related fatigue change from baseline and the percentage of patients with a clinically significant change in QOL measures failed to reveal any significant difference.[35]

The effect of methylphenidate on CRF in patients with advanced cancer was investigated by Bruera et al.[28] (table 1). In this study, stomach cancer was the most frequent type of cancer. Methylphenidate was given in doses of 5 mg every 2 hours, up to a maximum of 20 mg per day. The key end point was the median difference in FACIT-F fatigue at day 15. Secondary outcomes included anxiety, depression, and sleep. A total of 141 patients were eligible for evaluation. The FACIT-F fatigue scores of MP+NTI (median score, 4.5; P.005), PL+NTI (median score, 8.0; P.001), MP + CTI (median score, 7.0; P.004), and PL+CTI (median score, 5.0; P=.03) all improved from baseline to day 15. There were no significant differences in median FACIT-F fatigue improvement between the MP and PL groups (5.5 vs. 6.0; P =.69) or between all four groups (P .16). As measured by the ESAS, patients who took NTI had considerably better tiredness (P.001), nausea (P.01), sadness (P.02), anxiety (P.01), drowsiness (P.001), hunger (P.009), sleep (P.001), and a sense of well-being (P.001). Pedersen et al.[29] examined the methylphenidate as a possible treatment for fatigue in people with advanced cancer (table 1). In order to acquire 28 evaluable participants, a total of 38 patients were enrolled. Before taking the tablets, the average fatigue score was 75 for the placebo and 72 for the methylphenidate (0-100). The mean changes (decrease) for methylphenidate were 20 and 17, respectively, after two and five hours, compared to eight and five, respectively, for placebo. After two hours (P = 0.004) and five hours (P = 0.001), methylphenidate was considerably less effective than placebo. Methylphenidate was much more effective than placebo in relieving fatigue after two and five hours.

Mitchell et al.[30] investigated whether MPH reduces cancer-related fatigue in adults with advanced cancer (table 1). Because 43 patients completed 84 cycles of MPH and placebo in random order, considerably exceeding the sample size estimates, the sample size was surpassed. MPH had little effect on fatigue in general (mean difference 3.2; 95 percent credible interval -2.0, 9.0; posterior probability of favorable effect 0.890). On MPH, eight subjects improved significantly, whereas one participant's weariness worsened significantly. People who responded to MPH had no identifying traits from those who did not. MPH has no effect on fatigue in a group of adults with advanced cancer. The aggregated N-of-1 trial methodology is practicable, providing population-based sample estimates with a sample size less than half that of a parallel-group RCT. It also determined who responded to MPH and who did not, which is difficult to achieve in a standard RCT.

Roth et al.[33] investigated the efficacy of methylphenidate on

CRF in individuals with advanced prostate cancer and moderate to severe fatigue (Table 1). The patients were given methylphenidate 5 mg or a matching placebo on a "as needed" basis for six weeks. The dose can be increased up to 30 mg per day depending on the patient's response. When compared to the placebo group, the methylphenidate group experienced a significant decrease in BFI severity scores (p = 0.03) and a trend toward a bigger reduction in BFI total scores (p= 0.03).

Moraska et al.[35] published an intriguing study on the effects of methylphenidate on cancer-related fatigue. The experiment included patients with a history of cancer-related tiredness. Participants took one pill on days 1 through 7, two tablets on days 8 through 14, and three tablets on days 15 through 28. (see table 1) The final two weeks of the trial had a goal dose of 54 mg per day, which was met by taking 18 mg of methylphenidate per day. In the BFI's principal end outcome, there was no statistically significant difference between the methylphenidate and placebo arms. According to a subset study, patients with more acute fatigue and/or more advanced disease appeared to benefit from methylphenidate.

Lower et al.[36] studied the efficacy and safety of methylphenidate in the treatment of chemotherapy-related fatigue in patients in a randomized, double-blind experiment. The majority of the cancers studied were breast and ovarian, and the actual study did not specify the particular stages of disease progression. During an eight-week period, patients were given either methylphenidate (beginning at 5 mg twice a day and subsequently escalating to a maximum of 50 mg per day) or a placebo tablet that was equally matched (Table 1). When compared to placebo, methylphenidate-treated individuals in the FACIT-F showed a significant reduction in tiredness symptoms after eight weeks. An exploratory analysis identified significant variations in the FACT-F scores at a number of distinct time points.

Escalante and colleagues36 33 patients with breast cancer were randomly assigned to receive either 18 mg sustained-release methylphenidate or placebo once a day for two weeks before switching to the other treatment arm for another two weeks in this randomized placebo-controlled trial of cancer-related fatigue (table 1). The average age of the patients was 58 (range: 32-79), 30% had metastases, 82 percent were undergoing chemotherapy, 9% hormonal therapy, and 9% were receiving both chemotherapy and hormone therapy. On the Brief Weariness Inventory, the mean baseline score was 5.7 (range 4.1-8.6), suggesting significant exhaustion. Methylphenidate has been shown to improve verbal learning, memory, visual perception, analysis, and scanning speed. Methylphenidate, on the other hand, had no effect on the patients' severe levels of weariness or other symptoms, despite the fact that those who took it worked longer hours. Two-thirds of patients reported methylphenidate had helped them feel less tired at the end of the study, and more than half indicated they wanted to keep taking it. Methylphenidate was well tolerated, with no serious side effects.

According to the findings of this study, only three out of eleven methylphenidate trials had a significant effect on the primary outcome. [29,32,33] During the intervention period, some trials revealed a partial or trending positive effect. Several investigations demonstrated a significant effect in both treatment arms, with similar results in the placebo and intervention groups, showing that any pharmaceutical treatment has a considerable placebo effect. 32,33,37 Methylphenidate has been shown to reverse the sedating effects of opioids and reduce depressive symptoms[38], both of which contribute to fatigue.

Limitations of the study

This review had several limitations.

1. This is a narrative review without any meta-analysis.

2. Only RCT trials addressing the palliative phase were included, and some trials may have been left out, resulting in inefficiency being discovered in other pharmacological therapies or with different designs.

3. There were no trials that combined non-pharmacological and pharmacological therapies. Furthermore, the range of diagnostic methodologies makes it difficult to determine the impact of coexisting factors such as psychological, physical, and emotional health, as well as depression, on CRF.

CONCLUSION

To summarize up this study, cancer-related fatigue is a important clinical issue for cancer patients. Our findings suggest that methylphenidate may be useful in the treatment of CRF, but the evidence is inconclusive and has to be confirmed in a bigger study. All of the investigations, however, had tiny sample sizes. This information must be respected as conditional and temporary and provisional in the absence of convincing information from a single, expansive, well-conducted randomized controlled trial. To support and propose new research topics and interventions, more study into biological factors affecting weariness is required.

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