Review Article

Cancer and Non-cancer Fatigue Treated With Bupropion: A Systematic Review

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Abstract

Context. Fatigue is a predominant and distressing symptom in cancer and non-cancer conditions for which there is a paucity of recommendations for pharmacological interventions. Bupropion is a novel treatment whose efficacy and safety in the treatment of fatigue are unknown.

Objectives. This study aimed to systematically assess the evidence on the efficacy and safety of bupropion in the treatment of fatigue in people with cancer and non-cancer conditions.

Methods. PubMed, EMBASE, and Ovid Medline databases were searched up to July 26, 2022. Studies were included if they reported bupropion as an intervention for cancer and non-cancer-related fatigue and used an objective scale to assess symptom outcomes. Experimental and quasi-experimental studies in adult patients published in English were included.

Results. This review reports on seven studies (three randomized studies, three non-randomized studies, and one case series) that enrolled a total of 584 patients. Bupropion was tested in five studies for treating cancer-related fatigue and in two studies for treating fatigue in non-cancer conditions. The reviewed studies were heterogeneous in relation to the scales used to assess fatigue. Six out of seven studies reported that bupropion significantly reduced the fatigue burden without causing major adverse effects. These positive results must be taken with caution caused by the small sample sizes and low quality of the studies reviewed.

Conclusion. Bupropion may prove to be an effective and safe intervention for fatigue in cancer and non-cancer conditions. A high-quality randomized trial is warranted to test current preliminary results. J Pain Symptom Manage 2022;000:e1−e8.

Key Words

Palliative care, bupropion, symptom management, fatigue, cancer-related fatigue

Key Message

- Bupropion has been used for the treatment of fatigue in cancer and non-cancer conditions.
- Preliminary evidence suggests bupropion is an effective intervention for fatigue.
- Bupropion has a better safety profile than current interventions for fatigue.

Introduction

The Colombian National Cancer Institute has identified cancer-related fatigue (CRF) as one of the top five first-tier high−priority research areas.[1] Fatigue is the most common symptom in patients undergoing cancer treatment for advanced cancer and is a 'pervasive debilitating sensation' that affects patients' quality of life and social interaction.[2,3] It is an 'ever present feeling of abject weakness.'[3] Even cancer survivors may suffer from fatigue long after recovery.[2,4] The prevalence of

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CRF varies between cancer populations and assessment tools, but it has been reported as high as 100%.[5] Moreover, fatigue is reported to be a frequent symptom of several non-cancer chronic diseases. For instance, 32%−96% of patients with chronic obstructive pulmonary disease, 42%−82% with chronic heart failure, 13%−100% with end-stage renal disease, 43%−95% with acquired immune deficiency syndrome, 81% with multiple sclerosis, 43%−50% with Parkinson, 50% with primary biliary cirrhosis, and 14% with dementia may experience fatigue.[5,6,7] Sadly, fatigue is a ubiquitous, underreported, underrecognized, and undertreated problem.[2,8]

The unknown pathophysiology and the various fatigue phenotypes affecting the physical, emotional, and cognitive spheres, within and between different conditions, limit treatment options.[9] Several mechanisms underlying fatigue include serotonin dysregulation, vagal afferent activation, muscle metabolism alterations, hypothalamic−pituitary−adrenal axis dysfunction, circadian rhythm disruption, anemia, and cytokine dysregulation.[9,10] The latest versions of five international guidelines for CRF recommend exercise, energy conservation, psychological support, sleep optimization, nutrition, and complementary therapies as the best evidence-based interventions.[11] The pharmacological treatments currently studied, such as psychostimulants (methylphenidate and modafinil) and corticoids, have been questioned for the adverse effects they cause and the null or moderate benefit they show.[2,4,11−13] Nevertheless, the shortage of clinical staff, the limited availability of caregivers, and the access barriers to non-pharmacological interventions call for the investigation of new pharmacological alternatives.

Bupropion is an antidepressant that inhibits norepinephrine and dopamine reuptake; it is well tolerated, has a low abuse potential, and produces a stimulant-like effect as a member of the N-alkylated cathinone group.[14] Bupropion has been proposed as an option for fatigue treatment as it increases monoaminergic and dopaminergic tone, reduces tumor necrosis factor-alpha, and produces a concomitant antidepressant effect.[15] A 2015 Cochrane review on CRF treatments found only one case report and one quasi-experimental trial testing bupropion.[16] A recent network meta-analysis comparing different pharmacological interventions found paroxetine as the most promising treatment and did not find a difference between bupropion and placebo (SMD=−1.185, 95%CI: −3.016 to 0.646).[17] However, Chow et al.[17] did not include trials testing bupropion for treating fatigue in non-cancer conditions and their conclusions were based solely on two small single-centered randomized trials.[17] Before discarding bupropion as a feasible pharmacological intervention for fatigue, an in-depth review of the existing evidence is needed. We conducted a comprehensive systematic literature review on bupropion's efficacy and safety for cancer and non-cancer-related fatigue treatment.

Methodology

Objective

The primary aim was to systematically review all the available studies investigating the effectiveness of bupropion in patients experiencing fatigue. The secondary aim was to evaluate the side effect profile of bupropion.

Search Strategy

We developed a search strategy using Medical Subject Headings (MeSH) and keywords related to bupropion treatment for fatigue in non-communicable chronic diseases. We searched three databases (Medline, EMBASE, and PubMed) using the following search string: *(Fatigue OR chronic fatigue OR fatigue syndrome OR cancer-related fatigue OR terminal care OR palliative care) AND (Bupropion OR norepinephrine dopamine disinhibitory OR Bupropion Hydrochloride)*. The systematic review protocol was registered in Prospero CRD42022349833. The search results were downloaded into Endnote software to remove duplicates. Five reviewers (JEC, MFI, NM, LC, and SG) screened abstracts to ensure consistency in eligibility criteria and they reviewed the full texts of the articles whose abstracts had met the criteria. References from selected articles and expertś recommendations were also included. In the event of disagreements, consensus was reached through discussion among the reviewers. We have reported the results following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Fig. 1.).

Study Selection

Eligible studies had to 1) be published in a peer-reviewed journal before June 26, 2022; 2) include human participants over 18 years old who experienced fatigue caused by chronic degenerative diseases 3) report an intervention of more than one week with bupropion for symptom treatment; 4) be published in English; 5) use an experimental or quasi-experimental research design, and 6) examine treatment outcomes using a fatigue scale. Given that there is no universal definition of fatigue in chronic conditions apart from cancer, the National Comprehensive Cancer Network (NCCN) definition of CRF was used as reference in the literature search: "Cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not

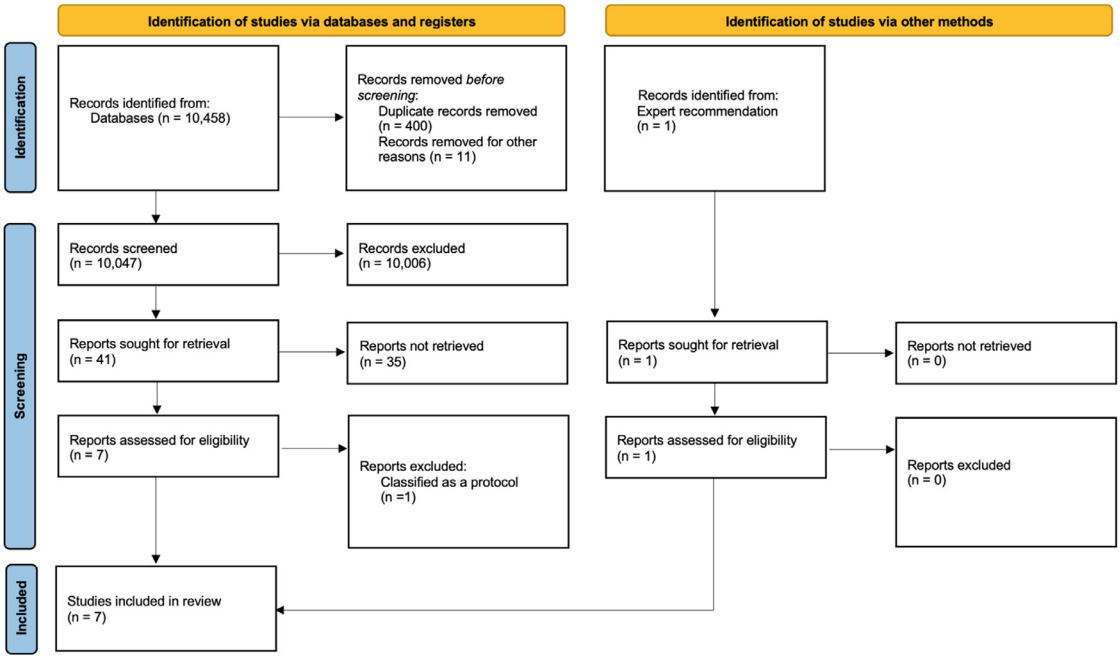

Fig. 1. PRISMA diagram.

proportional to recent activity and interferes with usual functioning".[2] Gray literature, editorials, commentaries, case series with ten or fewer patients, case studies, and protocols were excluded from the review.

Data Extraction

Two reviewers (EQ and SG) independently extracted data into a Microsoft Excel spreadsheet. Data extracted included the year of publication, country, study design, number of participants, inclusion/exclusion criteria, sample characteristics, type of disease, fatigue definition, fatigue assessment, bupropion intervention, comparator, time of follow-up, and efficacy and safety outcomes. To ensure consistency, extracted data were compared between reviewers, and disagreements were discussed until consensus was reached.

Quality Appraisal

Two reviewers (LC and MFI) independently assessed each included study for risk of bias. A third reviewer arbitrated possible differences. Randomized controlled trials were evaluated using the Cochrane Collaboration's Risk-of-Bias Tool 2, the Newcastle Ottawa Scale was used for evaluating non-randomized studies, and the Murad et al.'s tool for evaluating the methodological quality of case series.[18] No study was disregarded for its quality.

Data Synthesis and Analysis

We synthesized the characteristics of the randomized and non-randomized studies in a narrative summary. The primary outcome was fatigue improvement, which was reported using means (or difference in means) ± standard deviations or means with confidence intervals (CIs). The data for each type of study is presented regarding the efficacy and safety of the bupropion intervention. Epidemiological statistics were synthesized as they were reported in the reviewed articles. As a recent meta-analysis had been performed with two randomized studies,[17] the authors agreed not to perform a meta-analysis unless the search yielded new randomized trials for CRF treatment. In case of finding two or more randomized trials for treating fatigue in non-cancer conditions, a meta-analysis would be performed. All authors were involved in the analysis and interpretation of the results and vouched for their completeness and accuracy.

Results

The search process yielded 10,458 studies, of which 400 were duplicates, and 10,047 were deemed ineligible after screening titles and abstracts. One article was added following expert advice. Subsequently, the full texts of eight studies were screened in detail. Of these, one was a protocol and did not meet the eligibility criteria. Fig. 1 depicts the complete screening process. Seven eligible studies were included in the present review.[19–25] The publication dates ranged from 2004 and 2021 and the sample sizes from 15 to 230 participants. The median number of patients was 83. The length of follow-up ranged from 4 to 12 weeks, with a median of 7.2 weeks. The studies originated from four countries: Canada, the United States, Iran (n=2), and

Table 1
Clinical Trial's Risk of Bias Assessment

Study	Bias Arising From the Randomization Process	Bias caused by Deviations From Intended Interventions	Bias caused by Missing Outcome Data	Bias in Measurement of the Outcome	Bias in Selection of the 1	Total
Ashrafi, et al (2018)[20]	Low	Low	Low	Low	Low	Low
Salehifar, et al (2020)[19]	Low	Low	Low	Some concern	Low	Some concern
Barton (2021)[21]	Low	Low	Low	Low	Low	Low

Quality tool used: Cochrane risk-of-bias tool for randomized trials Version 2

Table 2
Quality Assessment of Cohorts and Cases-Control studies

Study	Type of Study	Selection	Comparability	Outcome / Exposure	Total
Moss, et al (2006)[22]	Cohort	Low	Low	Low	Low quality
Pardini, et al (2012)[24]	Case-control	Low	Low	Low	Low quality
Hashash, et al (2020)[23]	Cohort	Fair	Fair	Fair	Fair quality

Quality tool used: The Newcastle-Ottawa Scale

Table 3
Quality Assessment of Case series

Study	Selection	Ascertainment	Causality	Reporting	Total
Cullum et al (2004)[25]	Low	Low	Low	Low	Low quality

Quality tool used: Murad et al.'s tool.[18]

Italy (n=1). Three studies had a randomized design,[19,20,21] three were non-randomized open-label studies,[22–24] and one was a case series.[25] Overall, two randomized studies had a low risk of bias, and one had some concerns of bias. The non-randomized trials were of moderate (n=1) and low quality (n=2), and the case series was of low quality. Table 1–3 presents the quality details by type of study of the seven reviewed studies.

Efficacy Outcomes

The main characteristics of the studies are listed in Table 4. The randomized trials only included patients with CRF; however, CRF was evaluated in heterogeneous populations. Two trials examined CRF in patients receiving treatment at the time of the studies.[19,20] The remaining study investigated sexual desire and fatigue in cancer survivors who could or could not be receiving hormone therapy.[21] Patients on active treatment in the trials were 18 years or older, scored ≥4 out of 10 points on the Brief Fatigue Inventory (BFI), and had several types of cancer, including breast, gastric, prostate, liver, lung, pancreatic, ovarian, and hematologic neoplasms. Cancer stages were not specified.[19,20] Patients were excluded if they had a history of seizures; scored <50 points on the Karnofsky Performance Scale (KPS); had received psychostimulants, erythropoietin, or antidepressants in the last six weeks; were pregnant; had a rheumatologic condition, or had a renal or hepatic failure. Both trials used the BFI and Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale to assess CRF.

In the intervention arm of Ashrafi et al.'s study,[20] bupropion doses began with 75 mg for three days and were then titrated to 75 mg twice per day. The comparator arm of both trials was placebo. The primary outcome was CRF improvement; secondary outcomes were anxiety, depression, quality of life, and functionality improvement. Ashrafi et al.[20] found that bupropion improved CRF at week four (+7.0 ± 10.9 vs. +1.0 ± 10.9 [placebo] [$P < 0.000$]). Secondary outcomes, including depression and performance status, did not show a significant difference between groups. Salehifar et al.[19] found improved CRF levels in the bupropion group measured with the BFI at the end of week six (-1.8 ± 0.9 vs. -0.5 ± 0.7 [placebo] [$P = 0.006$]). For the FACIT-F scale, the mean fatigue scores for the bupropion group were better but without significant differences. The secondary outcomes favored bupropion intervention at six weeks, with improvement in anxiety and depression ($P < 0.001$) and performance status ($P < 0.001$).

In Barton et al.'s[21] randomized trial of cancer survivors, only patients with breast or ovarian cancer diagnoses were included. Patients were selected if they had a decreased libido as determined by desire subscale scores below 3.3 on the Female Sexual Function Index (FSFI). The primary outcome was sexual desire improvement with bupropion over placebo at week

Table 4
Characteristics of Bupropion Studies in Fatigue

Study	Number of participants	Population	Scale	Outcomes	Duration
Cullum et al (2004)[25]	15	Cancer	GCI	13 of 15 subjects reported fatigue improvement.	4 weeks
Moss et al (2006)[22]	21	Cancer	BFI	Decreased cancer-related fatigue (P <0.01) in both the depressed and not depressed group.	4 weeks
Pardini et al (2012)[24]	174	Multiple sclerosis	MFIS	Lower response to reward at baseline predicted higher rates of fatigue remission: (physical fatigue: r= -0.42, P<0.001; mental fatigue: r= -0.62, P<0.001; psychosocial fatigue: r= -0.51, P <0.001) in patients treated with bupropion.	12 weeks
Ashrafi et al (2018)[20]	57	Cancer	FACIT-F	Decreased cancer-related fatigue. (P<0.001)	4 weeks
Hashash et al (2020)[23]	52	Crohn's disease	MFI	Decreased cancer-related fatigue. (P< 0.02)	12 weeks
Salehifar et al (2020)[19]	30	Cancer	BFI FACIT-F	Decreased cancer-related fatigue. (P=0.006).	6 weeks
Barton et al (2021)[21]	230	Cancer survivors	PROMIS short form 8a	Fatigue interference with sexual function was not different between groups.	9 weeks

Abbreviations. BFI = The Brief Fatigue Inventory; FACIT-F = The Functional Assessment of Chronic Illness Therapy-Fatigue; MFI = Multidimensional Fatigue Inventory; MFIS = Modified Fatigue Impact Scale; GCI = Global Clinical Improvement; PROMIS = Patient-Reported Outcomes Measurement Information System.

nine with 150 mg or 300 mg extended-release daily dose. In the secondary outcomes, fatigue was assessed with the Patient Reported Outcomes Measurement Information System (PROMIS) fatigue scale. Neither dose showed a meaningful improvement in the primary or the secondary outcome. A meta-analysis could not be performed by including Barton et al.'s study[21] because the scales employed were different, and the CRF was appraised as a secondary outcome.

The non-randomized studies included non-cancer conditions such as Crohn's disease (n=1)[23] and multiple sclerosis (n=1)[24], as well as patients with cancer of the breast, head, neck, ovary, prostate, uterus, skin, and brain and lymphoma (n=2).[22,25] The primary outcome was fatigue improvement, but none of the studies measured fatigue using the same scale. In Pardini et al.'s[24] multiple sclerosis trial, fatigue was measured using the Modified Fatigue Impact Scale (MFIS), and the patients were included in the study if they had had a score of more than 38 points. In the Crohn's disease trial on sleep and fatigue by Hashash et al.,[23] the participants completed the Multidimensional Fatigue Inventory (MFI), and a cut-off score of 45 points was set as one of the inclusion criteria. In the studies with cancer patients by Moss et al. and Cullum et al,[22,25] the BFI and the Clinical Global Improvement (CGI) scale were used, respectively; the CGI was employed to assess fatigue improvement in addition to the severity of illness.[25]

The intervention dosages of bupropion in the four non-randomized studies were between 100 and 300 mg per day. The outcomes were followed for three months in the studies evaluating non-cancer conditions.[23,24] In the studies with cancer patients, bupropion intervention was evaluated after one and three months of treatment.[22,25] Bupropion significantly reduced fatigue, according to the four studies' results.[22–25] The Crohn's disease trial reported that the brief behavioral treatment of sleep and bupropion lowered the MFI mean score from 56.1 to 48.2 ($P \leq 0.001$) and improved sleep quality ($P \leq 0.001$). Anxiety and depression measured using the Hamilton Anxiety Rating Scale (HARS) and the Hamilton Depression Rating Scale (HDRS), respectively, also improved (HARS score 10.4 [preintervention] and 5.8 [postintervention], $P = 0.008$; HDRS score 9.0 [preintervention] and 5.0 [postintervention], $P = 0.001$).[23] Patients with multiple sclerosis had an improvement in fatigue scores from 47.4 ± 0.6 to 32.1±1.3 after bupropion therapy ($P <$ 0.001) and showed higher reward responsiveness than patients receiving escitalopram or placebo.[24] In the trial with cancer patients, bupropion significantly reduced BFI scores from 7.06 ± 0.95 to 5.14 ± 1.97 ($P = 0.01$).[22] This improvement was present in patients with and without depression. Patients with depression showed an improvement in HDRS scores from 23.0 ± 3.84 to 14.78 ± 8.79 ($P = 0.01$).[22] The case series study did not report a statistical analysis, but cancer patients treated with bupropion showed lower symptom burden up to two years after treatment.[25]

Safety Outcomes

In the randomized control trial on CRF by Salehifar et al.,[19] three patients were unwilling to continue in the study: two in the intervention group and one in the control group. No adverse effects were observed in

either group. In Ashrafi et al.'s[20] randomized control trial on CRF, 17 patients discontinued intervention caused by adverse events, consent withdrawal or loss to follow-up: nine in the intervention arm and eight in the placebo arm. Common and mild adverse effects were anorexia, constipation, nausea, dizziness, and abdominal or back pain. No severe adverse effects were documented, and there was no difference in adverse effects between both groups ($P = 0.11$). In the trial of Barton et al.,[21] women receiving 300 mg of bupropion once daily reported more headaches at week seven ($P = 0.01$). No toxicities were documented, and side effects were equally distributed across the 150 mg dose and the placebo arm.[21]

The non-randomized trials reported a low rate of patients lost to follow-up. Five patients with CRF and two fatigued patients with multiple sclerosis were lost to follow-up.[22,24] No patients missed or discontinued treatment in the Crohn's disease trial.[23] No adverse effect was reported in the three non-randomized trials.[22–24] The case series documented mild and limited cases of headaches, constipation, agitation, blur vision, confusion, pruritus, insomnia, and depression. No epileptic crisis was reported in patients with a history of seizures.[25]

Discussion

Fatigue is the most predominant and severe symptom in cancer patients in the last six months of life with a mean Edmonton Symptom Assessment System (ESAS) score of 6–8/10 points.[26] Caused by its concurrent occurrence and positive correlation with pain ($r = -0.20$, $P = 0.0012$), nausea ($r = -0.13$, $P = 0.04$), anxiety ($r = -0.27$, $P < 0.0001$), depression ($r = -0.19$, $P = 0.0019$), drowsiness ($r = -0.24$, $P = 0.0002$), dyspnea ($r = -0.17$, $P = 0.007$), anorexia ($r = -0.29$, $P < 0.0001$), and insomnia ($r = -0.25$, $P < 0.0001$), fatigue is usually underdiagnosed and undertreated.[27] Furthermore, there appear to be different phenotypes of fatigue depending on the cognitive or motor aspects caused by each chronic degenerative disease, making it challenging to investigate fatigue as a single entity.[28] Even placebo had a significant effect on CRF, obtaining a response rate of 29% (95%CI 25–32%) and an improvement of 4.88 points in the FACIT-F Scale score (95%CI +2.45 to +7.29).[29] These reasons partly explain the lack of consensus and recommendations on pharmacological treatments for fatigue. Previous pharmacological treatments, primarily stimulants, not only had a moderate response but implied a diversion risk.[13] The network meta-analysis by Chow et al. found paroxetine to be a promising pharmacological intervention for CRF.[17] In that same line, our systematic review is the first to comprehensively evaluate the literature on bupropion as a treatment for fatigue in cancer and non-cancer conditions. Even though the preliminary data is insufficient to draw conclusions, several findings must be underlined.

First, six out of seven studies showed a significant improvement in fatigue scores with bupropion over placebo in cancer and non-cancer conditions. The trial that did not show benefit of bupropion in fatigue had the limitation of assessing CRF as a secondary outcome in relation to sexual desire in cancer patients. Although the suboptimal quality of the studies cannot be overlooked, the favorable consistency of the results seems unlikely to be caused by a repeated bias incurred systematically by different authors. Second, bupropion's efficacy was explored in fatigue in non-cancer conditions, and promising results were found. In non-cancer conditions, fatigue is also a common symptom but is inadvertently ignored. The preliminary findings of bupropion reducing fatigue in two different autoimmune diseases are worth exploring in future trials. Third, bupropion was well tolerated and safe. The adverse effects were mild and limited; this characteristic alone could make physicians prefer bupropion over stimulants if the efficacy profile is similar or in special populations such as children and patients with a history of psychiatric disease or drug misuse. For these reasons, we believe a robust and high-quality randomized clinical trial is warranted to investigate the potential role of bupropion and other antidepressants in the treatment of fatigue in cancer and non-cancer conditions. Recently, a multicentered, randomized, double-blind, placebo-controlled, phase III trial protocol researching the efficacy of bupropion in reducing CRF in breast cancer survivors has been published. Also, it will explore the possible benefits of bupropion in depression and quality of life while reporting on the tolerability of the intervention. This trial aims to enroll 422 patients and is currently recruiting participants.[30] A breakthrough result from this milestone trial could transform our understanding and clinical practice of CRF.

Limitations

The review has a number of limitations that should be considered. The search was conducted only in three databases, in one language, and excluded grey literature; therefore, there is a chance of having missed relevant articles. However, the total number of screened articles was high enough to assure that the search was considerably extensive. Our results should be considered hypothesis-generating, given the low methodological quality and the design characteristics of the studies reviewed, especially regarding the non-cancer conditions caused by the paucity of current evidence. Moreover, both randomized trials with positive primary outcomes were single-centered and had a small number of participants (33 patients in total for bupropion

intervention).[19,20] Furthermore, the length of follow-up in the included trials only evaluated short-term ranges, which does not allow for assessment of the long-term effects of bupropion use. Also, bupropion's cost-effectiveness is unknown in fatigue treatment; this unexplored factor may favor or avoid bupropion use in clinical practice if its profile matches other pharmacological options. Future studies should be guided and interpreted through patients' reported outcomes. It is known that a clinically significant improvement in CRF is a reduction of approximately 10 points in FACIT-F and 4 points in ESAS fatigue scores.[31] In one study with bupropion, the FACIT-F score showed a change of 7 points[20]; this and other related outcomes should be analyzed in regard to patients' goals.

Conclusions

Fatigue is an ever-present symptom underdiagnosed and undertreated in chronic non-communicable diseases that places a significant burden on patients' quality of life. Bupropion is an atypical antidepressant, well tolerated and with a high safety profile, that has been considered a novel treatment for fatigue caused by its stimulant-like effect. The current studies of suboptimal quality that have used bupropion to treat fatigue in cancer and non-cancer populations have found significant efficacy. Still, the heterogeneous and quasi-experimental design of pilot studies limits their findings and warrants robust and high-quality randomized trials to confirm preliminary results. Future research should focus on pathophysiologic pathways, diagnosis, and treatment of fatigue in non-cancer conditions.

Submission Declaration

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