

Bupropion Sustained Release Treatment Reduces Fatigue in Cancer Patients

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Objective: To demonstrate that bupropion sustained release (SR) can reduce the symptoms of fatigue experienced by cancer patients.

Method: We studied an open-label case series of outpatients with fatigue referred for psychiatric assessment from a tertiary care cancer centre. Inclusion criteria were the presence of fatigue or depression with marked fatigue. Clinical status was assessed using the Global Clinical Improvement scale.

Results: Fifteen subjects with various cancer sites and psychiatric diagnoses were treated with bupropion SR (modal dose 150 mg) for up to 2 years. Most (13 of 15) saw improvement. Thirteen patients had minor, expectable side effects, and 10 patients were able to continue with bupropion for an extended time. All subjects who improved showed improvement within 2 to 4 weeks.

Conclusions: This is the first report that shows bupropion SR can reduce fatigue in cancer patients. Controlled studies with more homogeneous samples would be necessary to establish the efficacy of this intervention. Further studies should address whether this effect of bupropion is separate from its action as an antidepressant.

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Clinical Implications

- This is preliminary evidence that bupropion sustained release can reduce fatigue in cancer patients.
- Fatigue is a common, difficult-to-treat adjustment reaction for cancer patients following standard oncological treatment.

Limitations

- This is an uncontrolled case series.
- Confirmation of our results is needed through randomized, placebo-controlled studies.
- A formal assessment of the magnitude of depressive symptoms was not conducted.
- Generalizability of these findings is limited by the highly select patient population.

Key Words: bupropion, fatigue, treatment, cancer, clinical case series

Quality of life (QOL) issues are particularly important for cancer patients. Fatigue, which is generally difficult to treat (1–3), seriously interferes with QOL by substantially diminishing patient ability to carry out meaningful daily activities (4). There is considerable diagnostic confusion over cancer-related fatigue (CRF) in the literature (5). Depending on the sample of patients and the type of measure used,

prevalence estimates of fatigue during cancer treatment range from 25% to 99%. Between 17% and 30% of long-term survivors report problems with fatigue for several years after they complete treatment (6).

Atkinson and colleagues published a set of guidelines designed to assist in the identification and treatment of CRF (4). Cella and colleagues proposed a set of diagnostic criteria

for “Cancer-Related Fatigue Syndrome” that specifically consider CRF as distinct from major depression or somatoform disorders, but do not address the relation with adjustment disorder (7).

Interventions for the treatment of CRF are at an early stage of development and have followed those for the treatment of fatigue in noncancer populations. These have included both nonpharmacologic approaches (8) and pharmacologic agents, including psychostimulant drugs, especially methylphenidate (9–13). Hydrocortisone has been used in noncancer fatigue but not investigated in CRF populations (14). Several antidepressants, including fluoxetine (15–17), paroxetine (18,19), and mirtazepine (20,21), have shown effectiveness in treating depression in cancer patients. Fluoxetine (15,17) and paroxetine (19) have shown some promise in treating fatigue. The use of bupropion has been suggested but not reported (22–24).

Bupropion is an atypical antidepressant drug, chemically unrelated to tricyclic and tetracyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and other known antidepressant agents. Psychopharmacologically, it shares a wide range of actions with psychostimulants. The mode of action is believed to involve primarily dopaminergic and noradrenergic rather than serotonergic mechanisms (24–26). The safety of bupropion in humans has been extensively studied (27–29).

Bupropion has been used successfully in the treatment of attention-deficit hyperactivity disorder in adults (30–32) and children (33–37) and to increase the functional status of patients with depression (38). It has also been used to treat chronic fatigue syndrome (39,40), antidepressant-induced fatigue (41), and fatigue associated with multiple sclerosis (42). These lines of evidence suggest that bupropion is a stimulating drug with a unique mode of action making it suitable for the treatment of CRF. The effectiveness of bupropion in alleviating CRF has not been previously described and is the focus of this report.

Methods

Patient Characteristics

Cancer patients consecutively referred for psychiatric assessment at the Tom Baker Cancer Centre in Calgary were considered for bupropion treatment if they 1) had low energy as their presenting complaint ($n = 8$), 2) had clinically impairing fatigue following prior treatment with an SSRI ($n = 1$), and 3) identified fatigue out of proportion to other depressive symptoms in the clinical interview ($n = 6$). Subjects were excluded if they were receiving erythropoietin treatment, were in need of a blood transfusion, had a history or symptoms of diabetes, or had an active rheumatologic condition. Fifteen patients

were enrolled in the study. Their thyroid status was reviewed, and where necessary, thyroid-stimulating hormone levels were measured prior to treatment with bupropion. Prior antidepressant therapies were discontinued in all but a single instance (patient 2), and all other medications and over-the-counter preparations were held constant for the duration of the trial.

Table 1 shows the demographic information, the psychiatric and oncological diagnoses, and the current medications for each patient. After assessment and discussion of the risks (for example, occurrence of seizures) and potential benefits of bupropion treatment, all subjects gave informed consent for treatment and for publication of this report. If the psychiatric disorder exclusion criterion were disregarded, all subjects met Cella's criteria for CRF.

Treatment Program

In all patients, bupropion was started at 100 or 150 mg daily, and the dosage was adjusted according to the patient's response. Following treatment, subjects were rated for severity of illness and improvement of fatigue on the Clinical Global Improvement (CGI) scale (43) by a clinician not directly involved in these pharmacologic trials. Table 2 shows the initial severity of illness, the final dosage of bupropion, the side effects, and the CGI improvement score. Most subjects (13 of 15) reported some of the most common bupropion side effects, such as increased anxiety, dry mouth, nausea, insomnia, tremor, and tinnitus. These were rated as mostly mild to moderate.

Results

The degree of fatigue was rated in 6 subjects as very much improved, in 2 subjects as much improved, and in 5 subjects as minimally improved (Table 2). One patient showed no change, and a single patient reported feeling much worse (with respect to fatigue symptoms) following bupropion treatment. In total, 13 of 15 subjects reported improvement, with 8 rated as much improved or better. In all patients, the improvement occurred within 2 to 4 weeks.

Discussion

The case-series approach chosen for this study provided an opportunity to examine the effect of bupropion on the fatigue of a small number of cancer patients. The response in terms of decreased fatigue was often dramatic and prompt. For example, patient 1 presented for psychiatric evaluation following chemotherapy, complaining of persistent severe fatigue, increased anxiety, and irritability. Bupropion SR was started at 150 mg daily. When seen 15 days later, he reported significantly increased energy levels with a mild but tolerable increase in anxiety and insomnia that was managed by taking the medication as early in the day as possible. He was able to return to work

Table 1 Demographic and medication histories

Patient	Age (years)	Sex	Diagnosis			Medications	
			Cancer	Psychiatric	Previous	Current	Over the counter
1	42	M	Hairy-cell leukemia	Adjustment disorder with anxiety	Fluoxetine, moclobemide, zopiclone	None reported	None reported
2	51	W	Breast	Adjustment disorder with anxiety and depression	—	Clonazepam, paroxetine	Calcium, co-enzyme Q10, selenium, vitamin E
3	61	M	Oligodendroglioma	Mood disorder secondary to a general medical condition	Carbamazepine	None reported	None reported
4	58	W	Breast	Adjustment disorder with anxiety	Anastrozole, clodronate, melatonin, tamoxifen,	Acetaminophen, clonazepam, naproxen, zopiclone	Multivitamin
5	50	M	Oligodendroglioma	Adjustment disorder with depression	Phenytoin	—	Multivitamin
6	47	W	Leukemia	Major depression and panic disorder	Estradiol, lithium, lorazepam, medroxy-progesterone, nefazodone, risperidone, trazodone, zopiclone	Clonazepam, valproic acid	Calcium, chondroitin sulfate, glucosamine, multivitamin, spirulina
7	58	W	Uterine sarcoma	Adjustment disorder with anxiety and depression	St John's wort	Medroxy-progesterone	Calcium, garlic, multivitamin, vitamins C and E
8	87	W	Hodgkins lymphoma	Adjustment disorder with anxiety and depression	Codeine, digoxin, diltiazem, etidronate, lorazepam	None reported	Calcium, multi-vitamin, vitamin D
9	70	M	Prostate	Adjustment disorder with depression	Mitoxantrone	Atorvastatin calcium, dexamethasone, dilantin, diltiazem, leuprolide acetate, morphine, phenytoin, prednisone, rofecoxib	None reported
10	37	M	Oligodendroglioma	Depression not otherwise specified	—	Carbamazepine, phenytoin	Aspirin, multivitamin
11	40	W	Brain	Adjustment disorder with depressed mood	Dextroamphetamine, venlafaxine	Cimetidine, clobazam, clonazepam, lorazepam, prednisone, risperidone, vigabatrin	None reported
12	65	M	Lymphoma	Adjustment disorder with depression	None reported	Venlafaxine	None reported
13	54	M	Prostate	Adjustment disorder with anxiety and depression	—	Clonazepam, fosinopril sodium, hydrochlorothiazide	Acetaminophen; ibuprofen; vitamins A, C, and E; Chinese herbal with deer horn
14	56	W	Non-Hodgkins lymphoma	Adjustment disorder with depression	—	Acetaminophen, domperidone maleate, omeprazole magnesium, megestrol acetate	Calcium, multivitamin, vitamins B and C
15	69	W	Breast	Adjustment disorder with anxiety and depression	Nefazodone	Amitriptyline, celecoxib, codeine	Multivitamin, acetaminophen

Table 2 Outcome (CGI score)

Patient	Initial severity of mental illness	Global Improvement over the course of treatment	Final dose of bupropion (mg)	Side effects
1	Moderately ill (4)	Much improved (2)	150	Mild anxiety, insomnia
2	Markedly ill (5)	Minimally improved (3)	100	Severe headache
3	Markedly ill (5)	Very much improved (1)	150	None reported
4	Mildly ill (3)	Very much improved (1)	150	Mild anxiety, insomnia
5	Moderately ill (4)	No change (4)	300	Increased partial seizures, constipation
6	Moderately ill (4)	Minimally improved (3)	200	Moderate anxiety
7	Moderately ill (4)	Very much improved (1)	100	Dry mouth, mild agitation, irritability (at 150 mg)
8	Mildly ill (3)	Much improved (2)	200	Mild nausea
9	Moderately ill (4)	Minimally improved (3)	150	Mild constipation, hand tremors
10	Mildly ill (3)	Very much improved (1)	100	Hyperreflexia (transient)
11	Severely ill (6)	Much worse (6)	150	Mild nausea, blurred vision, confusion, depression
12	Moderately ill (4)	Very much improved (1)	200	None reported
13	Moderately ill (4)	Minimally improved (3)	300	None reported
14	Mildly ill (3)	Minimally improved (3)	250	Dry mouth
15	Markedly ill (5)	Very much improved (1)	150	Pruritis, headaches, tearfulness, sore eyes
Modal score	Moderately ill (4)	Very much improved (1)	150	

full-time. In other instances the response was slower. Patient 10, a 37-year-old man with oligodendroglioma, presented complaining of fatigue, poor concentration, and irritability. Bupropion SR was started at 100 mg daily. After a month of treatment, he reported improved attention and mood. Some hyperreflexia was also observed. Following 2 months of treatment, he reported excellent energy, improved concentration, and no problems with hyperreflexia.

Three subjects discontinued bupropion treatment because of side effects. A good example is patient 11, who reported feeling worse after bupropion treatment, with an increase in nausea, depression, and some blurring of vision. Bupropion was discontinued for lack of sustained response in 2 other subjects. Thus, 10 subjects were able to benefit from bupropion SR for up to 2 years. In examining the aggregate responses, there appeared to be no clear benefit in terms of fatigue symptoms for higher doses (200 to 300 mg) of bupropion over lower doses (100 to 150 mg). The major safety issue attributed to bupropion is the increased incidence of seizures (44). Although the frequency of seizures as a result of medication has been shown to increase in 1 out of 1000 people, this side effect is serious and must be monitored closely. In our case series, 1 patient with a history of grand mal seizures was on antiepileptic medication while taking bupropion and did not report an increase in the frequency of seizures. Another had a history of partial seizures, which were also controlled by medication. Upon initiating a trial of bupropion, the frequency of partial seizures reportedly increased but did not concern the patient, as it remained within the range of previous experience. The patient chose not to

increase antiepileptic medication to avoid the side effect of sedation as previously experienced.

The manufacturers of bupropion SR list seizure disorders as a contraindication for bupropion treatment and list factors that increase the likelihood of seizures as cause for extreme caution. This includes subjects with a central nervous system tumor. Unfortunately, there is no information on the risks to subjects who are on adequate dosages of antiepileptic medication, since all such subjects have been systematically excluded from studies sponsored by drug companies. Alternative drug therapies for fatigue, such as methylphenidate, amphetamines, and corticosteroids, all lower the seizure threshold. In addition, some antidepressants are associated with an increased rate of seizures that is comparable to, or higher than, that for bupropion SR—for example, venlafaxine (0.26%, product monograph) or fluoxetine (0.2%, product monograph).

Conclusion

Bupropion treatment appears to offer an alternative to currently available treatments for fatigue in select cancer subjects. Generally, bupropion is well tolerated. It has a low potential for abuse, and it is not a controlled substance. Future placebo-controlled studies with this medication are warranted, especially where subjects are evaluated with standardized fatigue inventories and symptoms of major depression are formally assessed by blinded raters. Studies in combination with nonpharmacologic approaches would be particularly useful.

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Résumé : Le traitement au bupropion à libération prolongée réduit la fatigue chez les patients cancéreux

Objectif : Démontrer que le bupropion à libération prolongée (LP) peut réduire les symptômes de fatigue que présentent les patients cancéreux.

Méthode : Nous avons étudié une série de cas ouverts de patients externes présentant de la fatigue et adressés à une évaluation psychiatrique d'un centre de soins tertiaires du cancer. Les critères d'inclusion étaient la présence de fatigue ou de dépression avec fatigue marquée. L'état clinique était évalué à l'aide de l'échelle d'amélioration clinique générale (GCIS).

Résultats : Quinze sujets ayant différents sièges du cancer et diagnostics psychiatriques ont été traités au bupropion à LP (dose modale 150 mg) pendant jusqu'à 2 ans. La plupart (13 sur 15) ont constaté une amélioration. Treize sujets sur 15 ont eu des effets secondaires mineurs prévisibles, et 10 ont été en mesure de continuer le bupropion sur une période prolongée. Chez tous les sujets qui se sont améliorés, cette amélioration s'est produite entre 2 et 4 semaines.

Conclusions : Ceci est la première étude qui révèle que le bupropion à LP peut réduire la fatigue chez les patients cancéreux. Des études contrôlées avec des échantillons plus homogènes sont nécessaires pour établir l'efficacité de cette intervention. Les futures études devraient déterminer si cet effet du bupropion est distinct de son action comme antidépresseur.