SCREENING

ELIGIBLITY CRITERIA: People who: a) are age 18 years or older, b) have a diagnosis of cancer, c) completed surgery, radiation, and/or systemic intravenous anticancer therapy (e.g., chemotherapy, targeted therapy, immunotherapy) 2 or more months prior to enrollment (ongoing oral hormonal, targeted, or maintenance therapy allowed; intravenous supportive therapy is allowed), d) stable disease or no detectable disease, e) report WORST level of fatigue in the past week as moderate to severe (i.e., a score ≥ 4 on a 0-10 scale), f) are able to read and speak English, and g) are capable of providing written informed consent

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CONSENT, BASELINE, AND RANDOMIZATION

SAMPLE SIZE: 422 patients will sign informed consent

BASELINE DATA COLLECTED: Demographic and clinical information, cancer-related fatigue and quality of life (FACIT-F/FACT-G), depression (PROMIS Depression Short Form 8a), cognition (PROMIS Cognitive Function 8a, Cognitive Abilities 4a), insomnia (ISI), symptom inventory (MDASI, symptom interference), blood draw (inflammatory markers, NF-kB gene expression, CYP2B6 genotype), saliva collection (cortisol)

RANDOMIZATION: Random (50/50) block of 4 or 8 stratified by study site; previous receipt of chemotherapy; metastatic disease at time of enrollment; and current receipt of oral hormonal, targeted, or maintenance therapy

Arm 1	Arm 2
Bupropion XL (150 mg/capsule)	**Placebo (lactose supplementation)**
Week 1: 1 capsule	Week 1: 1 capsule
Weeks 2-12: 2 capsules	Weeks 2-12: 2 capsules
Week 13: 1 capsule	Week 13: 1 capsule
Week 14: no capsules	Week 14: no capsules
N=211	**N=211**

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END OF STUDY ASSESSMENT

11-12 weeks after the start of the intervention

Cancer-related fatigue and quality of life (FACIT-F/FACT-G), depression (PROMIS Depression Short Form 8a), cognition (PROMIS Cognitive Function 8a, Cognitive Abilities 4a), insomnia (ISI), symptomatology (MDASI), adherence, dose reduction, early treatment discontinuation, blood sample (bupropion metabolites, inflammatory markers, NF-kB gene expression), saliva collection (cortisol)

3. CHARACTERISTICS OF STUDY POPULATION

3.1 Inclusion Criteria

Participants must:

3.1.1 Be at least 18 years of age.

3.1.2 Be diagnosed with cancer.

3.1.3 Have stable disease or no evidence of disease.

3.1.4 Report WORST level of fatigue in the past week as moderate to severe (i.e., a score ≥ 4 on a 0-10 scale, Screening Measures, question 1).[18, 78]

3.1.5 Have completed surgery, radiation, and/or systemic intravenous anticancer therapy (e.g., chemotherapy, targeted therapy, immunotherapy) 2 or more months prior to enrollment. Participants currently receiving oral maintenance, targeted, or hormonal therapy are eligible. Participants receiving intravenous supportive therapy (e.g., bisphosphonates) are eligible.

3.1.6 Able to read and speak English.

3.1.7 Currently not be pregnant or breastfeeding. Women of child-bearing potential must agree to use adequate contraception, i.e., abstinence, IUD (intrauterine device), hormonal contraceptive (birth control pills) or barrier method (condoms) prior to study entry and for the duration of study participation.

3.1.8 Be capable of providing written informed consent.

3.2 Exclusion Criteria

Participants must not:

3.2.1 Be receiving intravenous anti-cancer therapy (e.g., intravenous immune checkpoint inhibitor therapy, targeted therapy).

3.2.2 Be currently taking any medications that contain bupropion (e.g., Wellbutrin, Forfivo, Aplenzin, or Zyban).

3.2.3 Be taking an MAOI, linezolid, or methylene blue within two weeks prior to enrollment.

3.2.4 Be taking any anti-psychotic medications within a week prior to enrollment.

3.2.5 Have a history of renal impairment (i.e., glomerular filtration rate < 45).

3.2.6 Have a history of cirrhosis (i.e., Child-Pugh score ≥ 5).

3.2.7 Have a history of seizures.

3.2.8 Have a history of bulimia or anorexia nervosa.

3.2.9 Report a history of sensitivity to bupropion.

3.2.10 Report an allergy to lactose.

3.2.11 Have psychiatric or neurological disorder that would interfere with study participation per physician or physician's designee.