Fatigue is a highly distressing symptom of cancer associated with significant psychological morbidity and reduced quality of life. Cancer-related fatigue (CRF) has been underreported, underdiagnosed, and undertreated. Fatigue and depression may coexist in patients with cancer, and considerable overlap of symptoms often occurs. This has led researchers to examine the role of psychotropic medications to treat fatigue. Psychostimulants, wakefulness-promoting agents, antidepressants, and cholinesterase inhibitors have been studied for CRF treatment. Methylphenidate has been studied most and is effective and well tolerated despite common side effects. Some preliminary data support using modafinil for patients with CRF. Antidepressant studies have shown mixed results. Paroxetine shows benefit for fatigue, primarily when it is a symptom of clinical depression. Bupropion sustained release may have psychostimulant-like effects and, therefore, may be beneficial in treating fatigue. Donepezil, a cholinesterase inhibitor, has shown benefit only in open-label trials. Randomized, placebo-controlled trials with specific agents are needed to further assess the efficacy and tolerability of psychotropic medications in CRF treatment.