Cancer-related fatigue, quality of life, pharmacological treatment

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We agree with the concerns raised regarding the safety of amphetamines such as methylphenidate/dexmethylphenidate[1]. In fact, we generally support the use of non-pharmacological interventions, such as cognitive behavioral therapy or energy conservation and activity management, in all patients after the diagnosis of fatigue is made by one of the multiple tools available such as FACIT-F, Visual Analogue Scale, Chalder scale, Brief Fatigue Inventory[2], and others. If fatigue does not improve or if it is severe, pharmacological therapy should then be judiciously considered.

While the abuse potential of methylphenidate is an understandable concern, orally administered methylphenidate at doses prescribed for a therapeutic effect has few reinforcing properties[3]. In fact, psychostimulant abuse among patients with cancer-related fatigue has not been reported. Finally, a recent systematic review and meta-analysis evaluating psychostimulants for the management of cancer-related fatigue included 426 patients and found that there was no difference in the frequency of adverse events of methylphenidates. Placebo with a combined odds ratio of 1.24 (95% CI 0.42, 3.62)[4].

We agree that modafinil certainly may be considered an option for treatment-associated cancer-related fatigue (chemotherapy or radiotherapy), and recent evidence recommends its use in cases of severe fatigue and in patients with advanced disease[5-7]. However, evidence supporting the use of modafinil in mild or moderate fatigue does not exist. Although the authors state otherwise, they refer to a review article that makes no specific assertion regarding the use of modafinil according to fatigue severity, and primarily references the study by Jean-Pierre et al. that found modafinil to be effective only in severe fatigue[8].

Regarding the use of erythropoietin stimulating agents (ESA), our review described the recent evidence and recommendations on this topic thoroughly, including the concerns related to prothrombotic states and the recently raised possibility of ESAs stimulating tumor growth[9-12].

Guarana (*Paullinia cupana*) is a plant native to the central Amazon, known for its stimulant and aphrodisiac properties, and popular for its use in energy drinks[13,14]. In a randomized, double-blinded, crossover clinical trial published by our group, guarana demonstrated favorable effects on fatigue during chemotherapy[15]. The stimulant properties of guarana are generally taken to reflect the presence of caffeine, which comprises only 2.5%–5% of the extract's dry weight, although other purine alkaloids (theophylline and theobromine) are present in smaller quantities. The doses we used in this study (50 mg PO BID) would have negligible amounts of caffeine. Furthermore, no significant increase in cardiovascular events has been demonstrated in any study to date, but larger trials are needed to evaluate this promising therapeutic option for cancer-related fatigue.

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