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Comments, Observations, and Rebuttals

The Use of Pharmacological Preventive Therapy for Migraine With Weight Gain Potential Amid Coronavirus Disease 2019 Pandemic

We read with interest the narrative review by Arca et al[1] on the use of headache medicines, specifically non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, amid novel coronavirus disease 2019 (COVID-19) pandemic. Arca et al[1] have comprehensively summarized the current understanding on the risks and benefits of NSAIDs and corticosteroids to facilitate decision-making by the clinicians amid COVID-19 pandemic. Nevertheless, we feel that headache medicines including the tricyclic antidepressant amitriptyline and the anticonvulsant valproate that possess the potential for weight gain are also worthy of discussion.

It has been recently discovered that obesity may be the main driving factor in terms of the severity of illness with COVID-19.[2] To illustrate, a nationwide multicenter observational study in over 1,300 patients hospitalized for COVID-19 in France revealed that body mass index was the only variable positively associated with the primary outcome of combined tracheal intubation for mechanical ventilation and/or death within 7 days of admission (odds ratio = 1.28; 95% confidence interval 1.10-1.47) in multivariable analyses of covariates prior to admission.[3] In addition, a large retrospective database analysis of more than 3,000 individuals with COVID-19 in the United States revealed that those who had a BMI between 30 to 34 and >35 kg/m^2 were 3.6 times more likely to be admitted to critical care than individuals with a BMI <30 kg/m^2.[4]

In a 2010 systematic review of prospective double-blind, randomized controlled trials of medications for migraine prevention, the tricyclic antidepressant amitriptyline was effective for migraine prevention in four trials.[5] This had led to the listing of amitriptyline as probably effective for migraine prevention in the 2012 guideline from the American Academy of Neurology.[6] In fact, amitriptyline is the only tricyclic antidepressant that has proven efficacy for migraine prevention, with insufficient data regarding the other tricyclic antidepressants.[7] Nonetheless, amitriptyline also appears to be associated with the greatest amount of weight gain (0.4-7.3 kg) among the available tricyclic antidepressants.[8] In fact, amitriptyline was the only antidepressant with evidence of long-term weight changes (over 4 months or more) based on a comprehensive review and meta-analysis.[9] Weight gain effect of amitriptyline may be related to its ability to block histamine receptors and cause increased appetite.

A review of three trials evaluating valproate (divalproex sodium, sodium valproate, and valproic acid) for migraine prevention found that valproate was significantly more effective than placebo as measured by the number of patients experiencing at least 50% reduction in migraine frequency (odds ratio = 2.74; 95% confidence interval 1.48-5.08).[5] Despite its efficacy in migraine prevention, valproate has been associated with significant weight gain (0.7-6.9 kg), and the frequency of weight gain is up to 70% in the users of valproic acid.[8,10] Though the exact mechanisms driving weight gain from valproate are still unclear, insulin resistance and leptin resistance have been proposed as the principal mechanisms underlying weight gain with valproate.[10]

Therefore, the use of amitriptyline and valproate for migraine prevention may not be favorable amid COVID-19 pandemic due to its potential for weight

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gain which could lead to a worse prognosis shall patients hospitalized for COVID-19. In fact, the presence of obesity has also been previously associated with an increased frequency and severity of migraine headaches.[11-14] The acknowledgment of the potential for amitriptyline and valproate to cause significant weight gain will help in selection and modification of pharmacological therapy for migraine prevention during the COVID-19 crisis, especially for patients with comorbidities such as diabetes and hypertension who may be at risk of COVID-19 acquisition. More suitable therapeutic options for migraine prevention include the β-blockers metoprolol and propranolol, the serotonin-norepinephrine reuptake inhibitor venlafaxine, and the anticonvulsant topiramate.[6] These agents are either associated with negligible weight gain or associated with weight loss.[8,15]

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