








Venlafaxine can reduce the migraine attacks as well as amitriptyline: A noninferiority randomized trial

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Received 20 November 2021, Revised 18 January 2022, Accepted 27 January 2022, Available online 29 January 2022, Version of Record 10 February 2022.

<https://doi.org/10.1016/j.clineuro.2022.107151> Get rights and content

Abstract

Objectives

Migraine, as a primary headache, is among the leading causes of disability worldwide. The present study aimed at comparing the effects of [venlafaxine](#) (VLF) and [amitriptyline](#) (AMT) reducing the severity and the number of migraine attacks.

Methods

Patients with complaints of migraine attacks were randomly divided into two groups. The first group received [amitriptyline](#) at a dose of 25 mg every night, and the second group received [venlafaxine](#) at a dose of 37.5 mg daily. The duration of treatment was eight weeks.

Results

Eighty patients participated in the current study, out of which 57.5% were females. The mean age of the participants was 33 years, and the mean duration of disease was eight years. Both amitriptyline and venlafaxine significantly reduced the number of attacks per month (AMT: from 10.98 to 2.98, VLF: from 9.98 to 3.18), and six-item Headache Impact Test (HIT-6) score (AMT: from 67.78 to 49.73, VLF: from 66.65 to 48.88), and no significant difference was observed between the two [drugs](#). The results demonstrated no significant relationship between age or disease duration with the score of the HIT-6. The decrease rate in the score of the HIT-6 in males was higher than that of females which shows the modifier role of the gender. Besides, it is noteworthy to mention that the [adverse effects](#) of amitriptyline exceeded the venlafaxine among the patients.

Conclusion

The effectiveness of AMT and VLF in terms of their potential to reduce the intensity and duration of headaches was more noticeable in male patients than female patients. In terms of [adverse drug reactions](#), patients in the amitriptyline group complained more about [adverse drug reactions](#) (ADR) than patients in the venlafaxine group. It seems that in similar conditions, venlafaxine could have priority over amitriptyline in migraine prophylaxis.

Introduction

Migraine, which is distinguished by moderate-to-severe headache attacks with autonomic symptoms of the nervous system, is a type of recurring, chronic, and disabling neurovascular disorder. Its prevalence is 12% in the general population and has the second rank of disabling neurological disorders [1], [2], [3], [4].

Migraine headaches can be triggered by the susceptibility of the brain to a possible genetic-based imbalance in external and internal homeostasis. As a result of the so-called trigger, trigeminovascular system activation leads to the secretion of neuropeptides and other molecules, which are responsible for local inflammation and strengthening of the neural system in the brainstem, trigeminal nucleus caudalis, thalamus, and cortex. This process results in sensitization to pain, worsening of symptoms, and disability of the central descending inhibitory system in activating itself or controlling the headache attacks [5], [6]. Another substantially discussed

factor in the pathophysiology of migraine is cerebral and meningeal vasodilation, which can be affected by released mediators such as norepinephrine and calcitonin gene-related peptides. Furthermore, serotonin is of the mediators that are believed to play a key role in migraine pathophysiology with its possible low levels in-between the attacks and variable amount during attacks [4].

A various spectrum of medication is being utilized in the prophylaxis of migraine due to the fact that the current body of research lacks sufficient evidence over the underlying migraine headache mechanisms [5], [6]. Prophylactic treatment of migraine is predominantly aimed at reducing the frequency, duration, and severity of migraine attacks. Various considerations are taken into account over the selection of the medication, among which is the plausible side-effects of the prophylactic agent [5], [6], [7], [8]. Antidepressants are among the earliest types of medications with potential identified capabilities in preventing migraine attacks, particularly tricyclic antidepressants (TCAs) [9]. Amitriptyline (as a tricyclic antidepressant) is believed to have preventing mechanisms over the uptake levels of serotonin and norepinephrine. This characteristic simplifies the inhibitory effect in descending noxious such as endogenous pain control mechanisms that descend from the brainstem to the trigeminal nucleus caudalis. In addition, interacting with the endogenous adenosine system may inhibit the spreading of cortical depression [10]. Besides, due to the anticholinergic and antihistaminergic activities, it has the potential to justify its side effects. Sedation, weight gain, dry mouth, and constipation are among the most prevalent side effects of the so-called medications. Venlafaxine, a serotonin and noradrenaline reuptake inhibitor (SNRIs), was found effective in a double-blind placebo-controlled trial [11] and a separate placebo-controlled trial [12]. 5-hydroxytryptamine, norepinephrine, and dopamine re-uptake is being inhibited by Venlafaxine. Even though it possesses a comparable mechanism of action to the TCA's, it has the potential to further act expressly at the aforementioned receptors and does not bind the responsible receptors for the TCAs side effects [13], [14]. The current inquiry set out to put the prophylactic impacts and side effects of VLF and AMT into comparison in the individuals who suffer from migraine. The primary objective of the current trial was to evaluate AMT, as compared with VLF, for the prevention of headache frequency (attacks per month). The second objective was to gauge the effect of AMT, as compared with VLF, on attacks duration and intensity in migraineurs. The third objective was to compare the two study groups for any possible adverse drug reactions.

Section snippets

Study design

The current noninferiority randomized, double-blind trial was conducted between July 10, 2020, and April 30, 2021, in the neurology clinic of Imam Khomeini Hospital (Urmia-Iran). The study sample was chosen from a consecutive series of patients with chief migraine complaints.

Inclusion criteria: 1) patients suffering from migraine aged 18 to 60, 2) migraine criteria with or without aura based on the International Classification of Headache Disorders, third edition, β -version, 3) at least

Statistical analysis

The necessary sample size for the study was calculated using 35 subjects at 80% power and a significance level of 5% in each group. To this end, considering the dropout rate, 80 patients were classified into two groups randomly. SPSS V.22 was utilized in order to perform all the statistical analyses. Initially, the Kolmogorov-Smirnov test was used at the beginning of the analysis in order to ensure the normal distribution of the data. Paired samples t-test was utilized in order to investigate

Results

The first patient enrolled on July 10, 2020, and the last on April 30, 2021. Overall, 80 patients (40 in the VLF and 40 in the AMT group) completed the study period. There were no significant differences between the VLF and AMT groups regarding age, sex, disease duration, frequency of headache, and HIT-6 score at baseline. Demographic and clinical characteristics are presented in Table 1.

Discussion

The fundamental action to reduce the attacks' frequency, duration, and severity of migraines is prophylactic treatment. Various factors are involved in the selection of drugs for prophylaxis, such as possible side effects of the prophylactic agent [12], [14]. Several studies investigated the effect of amitriptyline and venlafaxine compared with placebo or other drugs [14], [16], [17], [18], [19]. However, to our knowledge, only one trial had compared AMT with VLF for migraine prophylaxis [12].

Conclusion

The results of the present study showed that both drugs provide clinically relevant benefits for migraineurs, attacks frequency, and HIT-6 score. These drugs reduced the intensity and duration of headaches in male patients more than that of female patients that were reported for the first time. In the point of adverse drug reactions, patients in the AMT group complained of ADR more than patients in the VLF group. It seems that in similar conditions venlafaxine can have a priority to

CRedit authorship contribution statement

Dear Chief Editor of Clinical Neurology and Neurosurgery. Our contributions for preparing this study. **Hedayat:** Conceptualization, Investigation and Writing – original draft. **Nazarbaghi:** Project administration, Investigation and Writing – review & editing. **Heidari:** Methodology, Software, Formal analysis, Data curation. **Sharifi:** Conceptualization, Methodology, Writing – review & editing, Supervision and Project administration.

Acknowledgments

The authors are inclined to state their appreciation to the Clinical Research Development Unit of Imam Khomeini Hospital, Urmia University of Medical Sciences, for English editing. The study was backed by the Urmia University of medical sciences. Urmia, Iran. The authors declare that they have no conflict of interest.

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