

Clozapine as add on therapy for difficult migraine patients

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Background: Difficult-to-treat migraineurs are frequently seen in tertiary centers. Although these patients pose a challenge to physicians, personnel and even other patients, underlying mechanisms and effective treatments are still uncertain. Neuroleptics such as quetiapine, chlorpromazine and others have been used although with poor evidence of its efficacy.

Objectives: The aim of this study is to evaluate whether the atypical neuroleptic clozapine, which acts on serotonergic, dopaminergic and noradrenergic systems, may help improve the treatment response to migraineurs who did not present headache frequency reduction of higher than 50% despite the previous use of numerous drugs.

Methods: It was an open study carried out in two headache clinics during the period of 2009-2012. Every migraineur, according to the IHS-II classification, who did not respond to at least 5 pharmacological preventive agents used alone or in combination, in addition to complain of sleep problems, was prospectively studied. Clozapine was added to patients already in use of other agents in a single daily dose at bedtime, starting with 12.5 mg and was titrated every 14 days to 25 mg and 37.5 mg. The dosages of the other pharmacological agents in use were not adjusted during the previous two months. A detailed headache calendar had to be filled by all patients.

Results: Eighteen patients (12 women, 6 men, ages 27-62 years, mean 45) were included and 15 completed the use of the drug. After 2 months (one month with 37.5 mg) the patients were evaluated regarding the decreasing of headache frequency of higher than 50%. The average headache frequency before the use of clozapine was 10 days/month and after was of 9.4 days/month. Adverse effects were reported by 12 (80%) and gaining weight, somnolence and drowsiness were the most reported events. Fever was presented by 3 patients. Two patients among the 15 did not reach 37.5 mg and remained with 25 mg/day due to fear of side effects.

Comments: It is not known why some headache sufferers do well with the use of neuroleptics. Psychiatric comorbidities don't seem to explain it since the dosages used are much lower than that for psychiatry. However, the modulatory effect of these drugs on various neurotransmitter systems may play a role. Despite the open methodology, clozapine does not seem to be useful for the prevention of migraine even as add on therapy. Controlled studies with higher doses are necessary to confirm these observations.

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