Topiramate plus nortriptyline in the preventive treatment of migraine: a controlled study for nonresponders

BACKGROUND:

- Preventive treatment for migraines with beta-blockers, antidepressants, or neuromodulators is recommended for patients with frequent or disabling migraine attacks.
- A sizeable proportion of migraine suffers on preventive treatment do not show an adequate response to prophylactic treatment with these a single first line agent.

OBJECTIVE:

- To see if patients with less than a 50% decrease in headache frequency with the use of a single agent could benefit from a combination regimen of a tricyclic antidepressant (nortriptyline) and a neuromodulator (topiramate).

METHODS:

- Design: Single site, randomized, blinded, parallel, placebo-controlled trial; Duration: 6 weeks
- Inclusion Criteria: Episodic migraine for at least 1 year classified according to the International Classification of Headache Disorder, less than 50% headache frequency improvement at 8 weeks from baseline prophylactic treatment, consideration by patients of a lack of benefit from their preventative migraine medication
- Exclusion Criteria: Women not using stable contraceptive methods for at least 3 months, patients with less than 4 or more than 12 headache days per month, any relevant comorbid psychiatric or medical conditions
- Primary Outcome Measure: Decrease in the number of headache days at 6 weeks, relative to baseline, comparing both groups
- Secondary Outcome Measure: Proportion of patients with at least 50% reduction in headache frequency at 6 weeks relative to baseline
- Total of 80 patients at start of study
    - 44 people received a combination of topiramate and nortriptyline
    - 17 people received topiramate plus a placebo
    - 19 people received nortriptyline plus a placebo
- Power 80% to detect a difference at a 5% significance level (assuming a SD of 1.5). This was calculated to be sufficient for 38 people per group.
- Data handling was per-protocol.

RESULTS:

- Number of subjects completing the study and used for analysis
    - 38 in the combination group
    - 14 in the topiramate + placebo group
    - 16 in the nortriptyline + placebo group
- Primary outcome measure:
    - The combination group had a significantly greater reduction in headaches compared to the placebo groups (4.6 reduction (SD1.9) vs 3.5 reduction (SD 2.3), p=0.04)
    - Differences between the topiramate and nortriptyline placebo groups were not significant

- Secondary outcome measure:
    - 78% of patients in the combination group had at least a 50% reduction in headache frequency
    - 47% of patients in the topiramate + placebo group had at least a 50% reduction in headache frequency
    - 37% of the patients in the nortriptyline + placebo group had at least a 50% reduction in headache frequency
    - The difference between the combination group and the placebo groups was significant with a p value of 0.04
- Authors' Conclusions: Patients who experienced incomplete relief with adequate doses of a single prophylactic agent showed significant reduction in the frequency of their headaches after receiving combination therapy with these agents.

STRENGTHS:

- Blinded, placebo-controlled study design
- Use of first-line, generically-available agents for the prevention of migraine
- Attempt at mimicking a "real-life" situation often seen in tertiary headache centers

LIMITATIONS:

- Follow-up only occurred once after 6 weeks when guidelines recommend monthly follow-ups over 12 weeks
- Low doses of the medications were used
- Reported information regarding the baseline characteristics within the groups was very limited
- Sample size was inadequate to ensure 80% power
- Variability not reported for all aspects of the study
- Use of a 1-sided t-test instead of a 2-sided
- Reasons for drop out were not reported
- Results were based on self-reported data that was collected monthly
- Large placebo effect exhibited
- Protocol for receiving initial treatment with either nortriptyline or topiramate was not reported or established.
- Side effect profiles between the two treatment groups were considerably different
- Extrapolation of the results would be difficult given limits of the population by the inclusion and exclusion criteria

CONCLUSION:

- Although the study showed that there was a statistically significant difference in the reduction of migraine headaches with combination therapy compared to the use of a single agent, this reduction may not be clinically significant. The combination group and placebo groups only differed by one headache reduction in 6 weeks while side effects were seen in 25% more patients receiving the combination therapy.
- Both of the agents studied in this trial are clinically useful in the preventing migraines, as are others. It would be more appropriate to allow an adequate trial of all of the possible preventative treatments available before trying a combination approach due to the possibility of additive side effects

- Future research:
    - A larger, more diverse population
    - Multi-center, randomized, cross over, blinded placebo-controlled design evaluating different combinations of all of the different first line prophylactic agents.
    - The subjects should attempt monotherapy with different agents for at least 12 weeks before enrolling for a definitive classification of an inadequate response
    - Follow-up should be conducted every 30 days over a span of 90 days.

REFERENCE: Krymchantowski AV, Jevoux CC, Bigal ME. Topiramate plus nortriptyline in the preventive treatment of migraine: a controlled study for nonresponders. J Headache Pain (2012) 13: 53-59

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