Metanx in Type 2 Diabetes with Peripheral Neuropathy: A Randomized Trial

BACKGROUND:

- In patients with diabetes mellitus, prolonged hyperglycemia can result in peripheral neuropathy (pain and/or loss of sensation in the extremities). Neuropathy issues may be related to vitamin B deficiencies; therefore, the supplementation of vitamin B_{12}, vitamin B_6, and folate (vitamin B_9) may improve diabetic peripheral neuropathy.

OBJECTIVE:

- To determine whether Metanx (L-methylfolate, methylcobalamin, pyridoxal-5'-phosphate) improves sensory neuropathy in patients with type 2 diabetes.

METHODS:

- **Design:** Multicenter, randomized, double-blind, placebo-controlled trial; Duration: 24 weeks.
- **Inclusion criteria:** 25-80 years of age with type 2 diabetes and neuropathy.
- **Exclusion criteria:** Peripheral vascular disease, amputation or ulceration within 2 years before screening, Charcot neuroarthropathy, previous surgery to spine or lower extremity with residual pain or impaired mobility, severe arthritis causing pain upon walking, A1C > 9% at screening, blood pressure > 160/90, uncontrolled asthma or shortness of breath within 2 months before screening, advanced renal disease (serum creatinine > 2.5 times the upper limit of normal), pregnant or nursing, history of alcohol or drug abuse within the past 3 years; no α-lipoid acid or B_{12} injection before screening, no more than 10 mg of B_6 or 800 µg of folate within 2 months before screening, no current treatment with systemic steroids, immunosuppressives, or radiotherapy.
- **Number of patients enrolled:** 214 patients (106 in the Metanx group, 108 in the placebo group) entered the study; however, 200 patients completed the study.
- **Drug regimen and dosage used:** Metanx (L-methylfolate calcium 3 mg, methylcobalamin 2 mg, and pyridoxal-5'-phosphate 35 mg) was compared to placebo.
- **Primary outcome measures:** Vibration perception threshold (VPT) on the great toe (hallux) of each foot.
- **Secondary outcome measures:** Neuropathic symptoms as evaluated by a modified 6-item Neuropathy Total Symptom Score (NTSS-6) and disability as measured by the Neuropathy Disability Score (NDS), plasma levels of folate and its active form, 5-methyltetrahydrofolate (5-MTHF), PLP, vitamin B_{12} and its metabolite methylmalonic acid (MMA), homocysteine, health-related quality of life as determined by the Medical Outcomes Short-Form 36-Item Health Survey (SF-36) and participants' lower-extremity pain perception measured using a 10-point visual analog scale.

RESULTS:

- **Primary outcome measure:** VPT was found to decrease in both groups and there was no significant difference in VPT between the Metanx and placebo groups (-1.96 ± 13.08 volts with Metanx, -3.27 ± 10.32 volts with placebo).
- **Secondary outcome measures:** Neuropathy symptoms were reported to improve in the Metanx group; however, symptoms also improved in the placebo group (3.73 ± 1.79 at baseline to -0.96 ± 1.54 at 24 weeks with Metanx, 3.45 ± 2.05 at baseline to -0.53 ± 1.69 at 24 weeks with placebo). SF-36 mental component subscale improved in the Metanx group from baseline (1.99 ± 8.57 change from baseline at week 24 with Metanx, -0.29 ± 8.48 change from baseline at week 24 with placebo). Plasma levels of folate, 5-MTHF (active form of folate), PLP (bioavailable form of B_6), and vitamin B_{12} increased in the Metanx group ($p \leq 0.0001$ for each value).
- **Authors' conclusion:** Metanx can improve neuropathy symptoms as well as quality of life in patients with type 2 diabetes and peripheral neuropathy. In addition, Metanx is a safe way to alleviate diabetic neuropathy symptoms in the short-term.

STRENGTHS:

- Study compound (Metanx) was identical to placebo.
- Multiple centers (6 research clinics and hospitals throughout the US).
- Patients were randomized to receive Metanx or placebo via a computer-generated randomization number list.

LIMITATIONS:

- Study was funded and conducted by Pamlab LLC, manufacturer of Metanx.
- Bias appeared to be present in how the results were presented and in the discussion of the results.
- Lack of information pertaining to why 14 patients did not complete the study and which treatment group these patients were previously enrolled.
- Lack of primary outcome data in the article (not all outcomes were presented in results section).
- Large variability in baseline values (especially duration of diabetes).
- Extensive exclusion criteria was used which may limit the generalizability of the results.
- Non-exclusion of patients with a vitamin B_{12} deficiency.

CONCLUSIONS:

- In clinical practice, Metanx may be beneficial in patients with a folate, vitamin B_{12}, or vitamin B_6 deficiency who have type 2 diabetes and peripheral neuropathy.
- Further research is needed to evaluate whether Metanx does have a beneficial effect on sensory neuropathy in patients who do not have a vitamin deficiency at baseline. In addition, a longer trial duration (e.g., one year) may help demonstrate whether this compound does have the effects the authors suspect.

Reference: Fonseca VA, Lavery LA, Thethi TK, Daoud Y, DeSouza C, Ovalle F, et al. Metanx in Type 2 Diabetes with Peripheral Neuropathy: A Randomized Trial. The American Journal of Medicine. 2013;126(2):141-149.

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