**Efficacy and safety of neurotrophic factor-based therapies in human randomized controlled clinical trials; applicability to the inner ear**

Hans GXM Thomeer, MD, PhD; Aren Bezdjian, MSc; Véronique JC Kraaijenga, MD; Dyan Ramekers, PhD; Huib Versnel, PhD; Sjaak FL Klis, PhD; Wilko Grolman, MD, PhD

**Authors’ affiliations:**

Department of Otorhinolaryngology and Head & Neck Surgery, University Medical Center Utrecht, Utrecht, the Netherlands.

Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, the Netherlands.

**Background**: The present review aims to determine the safety and efficacy of neurotrophic factor (NF)-based therapies in human trials and to assess applicability to the inner ear.

**Methods**: Articles were identified through Embase, Medline, Cochrane, and Global Health electronic databases. Two authors screened eligible articles using pre-defined inclusion criteria and extracted data after critical appraisal.

**Results**: From 2103 articles retrieved at the initial search, 20 randomized controlled trials encompassing 3974 patients were selected for data extraction. All included patients were adults (mean age ± SD: 55.2 ± 10.4 years). Amyotrophic lateral sclerosis (n=2090, 53%) was the most frequently reported indication for NF-based therapy, followed by diabetic polyneuropathy (n=1113, 28%). Ciliary neurotrophic factor, nerve growth factor, and insulin-like growth factor were most often used (n=1219, 50%; n=580, 24%; n=510, 21%; respectively). Injection site reaction was the most frequently occuring adverse event observed in 699 patients (61%), followed by asthenia in 436 patients (24%) and gastrointestinal disturbances in 372 patients (20%). Eighteen out of the 20 included trials deemed NF-based therapy to be safe, and 6 out of 17 studies assessing efficacy concluded the NF-based treatment to be effective. Non-neurodegenerative diseases treated by local deliveries of NFs were mostly considered safe and effective.

**Conclusions**: According to the present systematic review, NF-based therapies are considered safe in humans; however, they have yet to yield sufficient efficacy outcomes in treating human disorders. Translation and implementation from animal studies to human RCT in treating inner ear disorders seems safe and worthwhile and will be performed in our University Medical Center.