
Aims: In diabetic neuropathy, nerve conduction velocities are thought to decline by 0.5m/s/yr. We evaluated the electrophysiological changes in trials of pathogenetic treatments for diabetic peripheral neuropathy (DPN).

Methods: A literature search identified double-blind RCTs of ≥1 year duration from 1971 to 2017. Change in peroneal MNCV (PMNCV) and sural SNCV (SSNCV) and amplitude (SSNAm) were extracted from placebo and treatment arms.

Results: 19 trials were identified (placebo: n=2483, treatment: n=3260) with a duration of 68.7±37.3 weeks. One trial (placebo: n=10) in the decade 1980-1989, eleven trials (placebo: n=811) in 1990-1999 (DC1) and seven trials (placebo: n=1662) in 2000-2009 (DC2). In DC1 (placebo arm), PMNCV (0.33±0.9m/s/yr) and SSNCV (0.15±1.50m/s/yr) increased, while SSNAm (-0.09±0.63mV/yr) declined. In DC2 (placebo arm), PMNCV (-0.09±0.34m/s/yr), SSNCV (-0.03±0.96m/s/yr) and SSNAm (-0.13±0.15mV/yr) marginally declined. There was no difference between DC1 and DC2 in the placebo and treatment arms for PMNCV, SSNCV and SSNAm (p=NS for all). When evaluating all trials (n=19), both PMNCV and SSNCV increased in the placebo arm (0.17+0.6m/s/yr and 0.09±1.09m/s/yr respectively), while SSNAm showed a small reduction (-0.11±0.24mV/yr) (p=NS for all). There was only a marginal improvement in electrophysiology in the treatment arm compared to placebo (PMNCV 0.6±1.29m/s/yr, SSNCV 0.52±1.05m/s/yr, SSNAm 0.79±0.98mV/yr, p=NS for all).

Conclusions: The failure of clinical trials in diabetic neuropathy may be related to the improvement in electrophysiology in the placebo arm over time. A detailed analysis of the study demographics is merited to clarify factors that lead to a lack of placebo worsening. The use of electrophysiology as a surrogate end point for DPN a predominately small fibre pathology warrants candid discussion.