Efficacy of Placebo/Sham Interventions in Diabetic Peripheral Neuropathy: Lessons Learned from Systematic Review of Placebo-Controlled Clinical Trials

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Abstract

Background: Knowledge about placebo as a psychological phenomenon is not new, the use and misuse of placebo in practice and research had been demonstrated in its role for treating patients with most 'difficult-to-treat' conditions such as chronic pain syndromes and neuropathic pain. **Objective:** To evaluate the placebo-controlled trials in order to explore the placebo-related responses among patients with Diabetic peripheral neuropathy (DPN). **Methods:**A systematic review was performed using search terms "diabetic neuropathy, placebo/sham" in PubMed, CINAHL and Google Scholar to identify relevant studies.Descriptive data extraction and synthesis was done to organize studies according to comparison interventions- pharmacological and non-pharmacological; administered individually and/or in combination treatment of DPN population. **Results:** Of the final list of 56 included studies,there were five studies comparing placebo with non-pharmacological interventions which were on electrotherapy modalities in physical therapy namely static magnetic field therapy (n=1), Anodyne light therapy-monochromatic infrared photoenergy (n=3), microcurrent electrical stimulation (n=1). 51 studies had compared placebo with pharmacological interventions that used combination therapy (n=3) and individual drugs administered either orally (n= 42), intravenously (n= 1), transdermally (n= 2) or topically (n= 3). **Conclusion:** There was prevalence of treatment-responders in Placebo groups in clinical trials of DPN on drug monotherapy whereas placebo was not effective against combination drug therapy. The study findings suggest an important role of placebo in research and practice of DPN. Evidence for placebo responses for non-pharmacological interventions such as exercise therapy and/or manual therapy was not found.

Keywords: Placebo and nocebo; Psychosocial factors; Psychiatric neurorehabilitation; Clinical trials.

Introduction

The multidimensional role of mind in human behavior influences a person's knowledge, attitudes, beliefs and experiences in health and disease.[1] Healthcare and its adequate delivery requires patients/ clients and their caregivers to co-operate with healthcare professionals in a shared decision-making process.[2]

Patients' perceptions determine their report of success with treatments which is often meaured using self-reported outcome measures such as pain intensity, activity limitations and

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quality of life assessments.[3] Patients' reports in turn influence a particular clinical procedure's therapeutic effects, efficacy and effectiveness, which depend upon an individual's perceptions.[4]

Perceptual processes involving therapy and its delivery either positive or negative, directly and indirectly influence the experience and reported outcomes, the situations of placebo and nocebo.[5] Placebo was anecdotally considered a misnomer and was regarded to be a medical stigma due to the ethical issues involved.[6] More recently, placebo and nocebo are widely regarded as potential confounders in healthcare practice, education, research and administration.[7]

Although knowledge about placebo as a psychological phenomenon is not new, the use and misuse of placebo in practice and research had been highlighted in its role for treating patients with most 'difficult-to-treat' conditions such as chronic pain syndromes.[8]

Neuropathic pain being an important subset of people with chronic pain is the leading cause for psychosocial disturbances due to pain and bears huge impact on individual and society alike.[9] Diabetes is the leading cause for neuropathy[10] and neuropathic pain is the commonest complication following diabetes mellitus, the condition is termed as diabetic peripheral neuropathy (DPN) while the pain is denoted as diabetic peripheral neuropathic pain (DPNP).[11]

Previous scientific reports had analyzed placebo-specific responses in neuropathic pain clinical trials[12,13] but not on DPN or DPNP per se, and thus there is a need to evaluate the placebo-controlled trials in order to explore the placebo-related responses among patients with DPN.

Methodology

A systematic review was performed using search terms "(diabetes [Title] OR diabetic [Title]) AND (neuropathy [Title] OR neuropathic [Title]) AND (sham [Title] OR placebo [Title]) NOT autonomic [Title]" in PubMed, CINAHL and Google Scholar to identify studies published in English, with abstracts. The search was independently performed by two testers and consensus was adopted to solve disagreements in presence of third tester. A three-level scrutiny of obtained citations based upon title, abstract and full text content was done to identify relevant studies and descriptive data extraction and synthesis was done to organize studies according to comparison interventions- pharmacological and non-pharmacological; administered individually and/or in combination treatment of DPN population.

Results

Final list of 56 included studies were used for data extraction and synthesis. There were five studies comparing placebo with non-pharmacological interventions which were on electrotherapy modalities in physical therapy namely static magnetic field therapy (n=1), Anodyne light therapy- monochromatic infrared photoenergy (n=3), microcurrent electrical stimulation (n=1). There were 51 studies comparing placebo with pharmacological interventions that used combination therapy (n=3) and individual drugs administered either orally (n= 42), intravenously (n= 1), transdermally (n= 2) or topically (n= 3). The studies were descriptively reported as follows:

Non-Pharmacological Management V/s Electrical Modalities

V/s Static Magnetic Field Therapy:

Weintraub *et al*[14] studied the efficacy of multipolar, static magnetic (450G) shoe insoles in their randomized, placebo-control, parallel study of 375 subjects with DPN who were randomly assigned to wear constantly magnetized insoles or placebo who wore similar, unmagnetized device. The placebo(sham) treatment produced -3%

(burning), +1% (tingling and numbness), and -4% (exercise-induced foot pain). For a subset of patients with baseline severe pain, placebo produced 14% change in numbness and tingling and 21% change in foot pain at 4-months.

V/s Anodyne Light Therapy (Monochromatic Infrared Photoenergy)

Lavery *et al*[15] determined the efficacy of anodyne monochromatic infrared photo energy (MIRE) in-home treatments in their double-blind, randomized, sham-controlled clinical trial of 60 patients (120 limbs) two treatment groups: active or sham treatment. There were no significant differences in measures for quality of life, MNSI, VPT, SWM, or nerve conduction velocities in active or sham treatment groups ($P > 0.05$).

Leonard *et al*[16] determined the efficacy of ATS to decrease pain and/or improve sensation in their sham-controlled, double-blind trial of twenty-seven patients whose lower extremity was treated for 2 weeks with sham or active ATS, and then both received active treatments for an additional 2 weeks. Sham treatments did not improve sensitivity to the SWM, or the other clinical measures compared to ATS treatments.

Clifft *et al*[17] determined the effect of monochromatic infrared energy (MIRE) on plantar sensation in subjects with diabetic peripheral neuropathy in their randomized, double-blind, placebo-controlled study of 39 DPN subjects who received 30 min of active or placebo MIRE three times a week for 4 weeks. Placebo group also increased the average number of sites that patients could sense the 5.07 monofilament. Placebo group also produced early and overall significant gains which was not significantly different from the active group.

Microcurrent Electrical Stimulation

Gossrau *et al*[18] assessed the effect of micro-TENS in their placebo-controlled, single-blinded, and randomized study of 22 patients who were treated with micro-TENS therapy and 19 patients who had been treated with placebo therapy. Greater number of patients (10/19) in placebo group had a minimum of 30% reduction in NPS and 25% reduction of PDI score respectively.

Pharmacological Management

Individual Drugs

V/s ABT-594

Rowbotham *et al*[19] evaluated the safety and analgesic efficacy of ABT-594 (neuronal nicotinic acetylcholine receptor (NNR) agonist) in 266 patients who were randomized 1:1:1:1 to receive placebo, ABT-594 150 microg BID, ABT-594 225 microg BID, or ABT-594 300 microg BID. (placebo, -1.1; 150 microg BID, -1.9; 225 microg BID, -1.9; 300 microg BID, -2.0). The proportion of patients achieving at least a 50% improvement in the average diary-based PRS was greater in all three ABT-594 treatment groups. However, adverse event (AE) dropout rates were significantly higher in all three ABT-594 treatment groups (28% for 150 microg BID, 46% for 225 microg BID, and 66% for 300 microg BID) than for the placebo group (9%).

V/s Acetyl-L-Carnitine

Sima *et al*[20] evaluated databases from two 52-week randomized placebo-controlled clinical diabetic neuropathy trials testing two doses of acetyl-L-carnitine (ALC): 500 and 1,000 mg/day t.i.d and found that intention-to-treat amounted to 1,257 or 93% of enrolled patients with ALC treatment being efficacious in alleviating symptoms, particularly pain, and improved nerve fiber regeneration and vibration perception in patients.

De Grandis and Minardi[21] assessed the efficacy and tolerability of acetyl-L-carnitine (levacecarnine; LAC) versus placebo in the treatment of diabetic neuropathy, in their multicentre, randomised, double-blind, placebo-controlled, parallel-group study of 333 patients who were randomised to treatment with LAC or placebo. Placebo-treated group

showed improvements in sural sensory nerve conduction velocity (SNCV) by +1.0 m/sec, ulnar nerve SNCV by +0.1 m/sec respectively, whereas the improvements in amplitude occurred for the motor peroneal nerve by +0.1 mV). 8% of placebo-treated patients had reduced VAS scores at 12-months.

V/s Alpha Llipoic Acid

Reljanovic *et al*[22] randomly assigned Type 1 and Type 2 diabetic patients with symptomatic polyneuropathy to three treatment regimens: (1) 2 x 600(mg of TA (TA 1200), (2) 600)mg of TA plus placebo (PLA) (TA 600) or (3) placebo and placebo (PLA) to evaluate the efficacy of antioxidant thioctic acid (TA) and found that place group had improved tibial motor nerve conduction velocity by 1.5 +/- 2.9 m/s, while the other parameters such as sural SNCV and sural SNAP were better in treatment groups at 24 months follow-up.

V/s Becaplermin (Human Platelet-Derived Growth Factor-BB)

Wieman *et al*[23] compared the efficacy and safety of topically applied recombinant human platelet-derived growth factor-BB (rhPDGF-BB) (becaplermin) in their multicenter double-blind placebo-controlled phase III trial that included 382 patients with type 1 or type 2 diabetes and chronic ulcers of at least 8 weeks' duration who were randomized to receive becaplermin gel 30 micrograms/g, becaplermin gel 100 micrograms/g, or placebo gel and found becaplermin gel 100 micrograms/g increased the incidence of complete wound closure by 43% and decreased the time to achieve complete wound closure by 32%.

V/s Cannabis-Based Medicinal Product (Sativex)

Selvarajah *et al*[24] assessed the efficacy of Sativex, a cannabis-based medicinal extract, in their randomized controlled trial of 30 subjects with painful DPN received daily Sativex or placebo and found significant improvementsin pain scores in both groups, with between-group mean change being not significant, with a confounding effect of depression.

V/s Clonidine (Transdermal)

Zeigler *et al*[25] in their randomized, double-blind, crossover study of 24 patients administered transdermal clonidine, 0.3 mg/day, or placebo patches, each for 6 weeks and found that mean daily pain scores for the 6th week, the primary outcome variable, averaged 13% lower with clonidine than with placebo though it was not statistically significant.

Byas-Smith *et al*[26] conducted a clinical trial of transdermal clonidine in DPN patients using a 2-stage enriched enrollment design. In the first stage, 41 DPN patients completed a randomized, 3-period crossover comparison of transdermal clonidine (titrated from 0.1 to 0.3 mg/day) to placebo patches. Twelve responders from stage I entered into the 'enriched enrollment' second stage, consisting of an additional 4 double-blind, randomized, 1-week treatment periods with transdermal clonidine and placebo. Placebo did not differ much from clonidine during stage I but was not much for the stage I responders with clonidine in stage II.

V/s Cyclandelate

Heimans *et al*[27] performed a double-blind, placebo-controlled, cross-over study in 40 diabetic patients who were administered with cyclandelate in a dose of 1600 mg daily and found no positive effect on all clinical and electrophysiological outcomes compared to placebo.

V/s Dexomethorphan

Nelson *et al*[28] carried out a randomized, double-blind, crossover trial comparing six weeks of oral dextromethorphan to placebo in 14 and 13 patients with DPN respectively. In diabetic neuropathy, dextromethorphan decreased pain by a mean of 24% relative to placebo.

V/s Desipramine

Max *et al*[29] compared a 6 week course of desipramine (mean dose, 201 mg/day) to active placebo in 20 patients with painful diabetic neuropathy in their double-blind crossover trial. Two patients in placebo also reported at least moderate relief which tended to be greater in depressed patients.

V/s Duloxetine

Gao *et al*[30] assessed the efficacy and safety of duloxetine in 215 Chinese DPN patients in their double-blind, randomized, placebo-controlled study duloxetine 60 mg to 120 mg once daily or placebo for 12 weeks. Placebo produced similar pain improvements compared to DLXDuloxetine-treated patients more at 8th and 12-weeks post-treatment. The adverse events reported by Duloxetine-treated patients were nausea, somnolence, anorexia, and dysuria which were more than that for placebo.

Goldstein *et al*[31] examined the efficacy and safety of duloxetine, in their 12-week, multicenter, double-blind study of 457 patients who were randomly assigned to treatment with duloxetine, or placebo. The placebo group responses were not better compared to the drug-treated group.

Kajdasz *et al*[32] performed a post hoc analysis to summarize the efficacy and tolerability of duloxetine where the data was pooled from three 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies in which patients received 60 mg duloxetine either QD or BID or placebo.

Raskin *et al*[33] in their multicenter, parallel, double-blind, randomized, placebo-controlled trial of 348 DPN patients who were randomly assigned to receive duloxetine 60 mg once daily (QD), duloxetine 60 mg twice daily (BID), or placebo, for 12 weeks. Compared with placebo-treated patients, both duloxetine-treated groups improved on the 24-hour average pain score. The placebo-treated group had lesser adverse event-related dropouts (2.6%) than the Duloxetine groups (12.1%).

V/s Epalrestat:

Goto *et al*[34] evaluated the clinical efficacy of epalrestat, an aldose reductase inhibitor in 196 DPN patients in their double-blind study using placebo as a control for 12 weeks. The placebo produced 12% disappearance rate of upper limb spontaneous pain and 22.6% for lower limb spontaneous pain.

V/s Fidalrestat

Hotta *et al*[35] evaluated the efficacy of fidarestat, a novel aldose reductase (AR) inhibitor, in a double-blind placebo controlled study in 279 patients who were treated with placebo or fidarestat for 52 weeks. In the placebo group, no electrophysiological measure was improved, but one measure significantly deteriorated (i.e., median nerve FCV).

V/s Gabapentin

Backonja[36] administered gabapentin in escalating doses (up to 3600 mg per day) to eligible patients in a double blind placebo controlled study and found that Placebo didnot show better pain relief than that of Gabapentin.

V/s Gamma-Linolenic Acid

Jamal and Carmichael[37] studied 22 patients in their double-blind, placebo-controlled study which assessed the effect of dietary supplementation with gamma-linolenic acid who randomly received either 360 mg gamma-linolenic acid (12 patients) or indistinguishable placebo capsules (10 patients) for 6 months. The placebo group did not improve in neuropathy symptom scores, nerve conduction velocity studies, and sensory perception thresholds compared to active group.

V/s Glyceryltrinitrate

Agrawal *et al*[38] in their double-blind randomized placebo-controlled study evaluated the safety and efficacy of sodium valproate and glyceryltrinitrate (GTN) in 83

DPN subjects who were given either sodium valproate and GTN spray (group A) or placebo drug and GTN spray (group B) or sodium valproate and placebo spray (group C) or placebo drug and placebo spray (group D). The placebo drug and placebo spray (groups B and C) also experienced significant improvement in pain scores along with electrophysiological parameters than the all-placebo group D.

Agrawal *et al*[39] tested the effectiveness and safety aspect of glyceryltrinitrate (GTN) in the management of DPN in their Randomized double blind placebo controlled cross-over study of 48 patients who were given either drug (group A) or placebo (group B) in the first phase which lasted for 4 weeks, followed by 2 weeks wash out period and thereafter receiving 4 weeks of cross-over regimen. Both groups A and B experienced significant improvement in pain score in their drug phase of trial, when compared to placebo phase of other group.

V/s Isosorbidedinitrate Spray

Yuen *et al*[40] examined the effects of isosorbidedinitrate (ISDN), in their double-blind, randomized, placebo-controlled, and two-period cross-over design of 22 diabetic patients who were randomized to receive ISDN or placebo sprays for 4 weeks, exchanging their treatment for a further 4 weeks after a 2-week wash-out period. At study completion, 4 patients reportedly preferred the placebo spray instead of the active one.

V/s Ketamine (Topical)

Mahoney *et al*[41] undertook a randomized, placebo-controlled, double-blind study to determine the efficacy of topical 5% ketamine cream in 17 DPN patients who applied 1 mL of either ketamine cream or placebo cream for 1 month and found that placebo had similar effect of improvement on pain.

V/s Lacosamide

Wymer *et al*[42] studied the efficacy of lacosamide at a daily dose of 400 mg/d in their multicenter, randomized, placebo-controlled, double-blind trial which consisted of a 2-week run-in period, a 6-week titration phase, and a 12-week maintenance phase, during which patients received placebo or fixed doses of lacosamide 200, 400, or 600 mg/d and found that 46% of placebo-treated patients achieved at least a 2-point or 30% reduction in Likert pain score, and only 9% of patients dropped out in the placebo group.

Shaibani *et al*[43] evaluated the efficacy and tolerability of oral lacosamide (200, 400, and 600 mg/day) in patients with painful diabetic neuropathy in a double-blind, randomized, placebo-controlled trial and found that endpoint reductions in mean pain score were higher with all doses of lacosamide, producing early-onset effect with significant reductions over placebo during the titration period.

Rauck *et al*[44] ascertained the effect of lacosamide on 119 DPN patients in their multicenter, randomized, double-blind, placebo-controlled trial where Lacosamide (N=60) was titrated from 100 to 400 mg/d or maximum tolerated dose and placebo (N=59) were the administered interventions. There were 11 dropouts in placebo group compared to 14 dropouts in drug group and there were no adverse events in 15 placebo participants versus 8 drug participants. 22%, 8% and 7% of placebo-treated patients had adverse events of headache, dizziness and nausea respectively.

V/s Lipo-PGE1 (Prostaglandin E1)

Toyota *et al*[45] compared the effect of lipo-PGE1 (10 micrograms/day) with placebo in two studies (double-blind and well-controlled) which enrolled 364 diabetic patients with neuropathy and/or leg ulcers and found that clinical improvement was noted in 30.0% of the placebo group in Trial 1.

V/s L-Arginine

Jude *et al*[46] investigated the effect of L-arginine on endothelial function, transcutaneous oxygen and clinical neuropathy in 30 DPN patients who were randomized to receive L-arginine (3 g three times daily) or

placebo (3 g three times daily) for 3 months. No difference was observed between drug-treated and placebo-treated groups on all measures.

V/s Lamotrigine

Vinik *et al*[47] assessed the efficacy and tolerability of lamotrigine in two replicate randomized, double-blind, placebo-controlled studies on patients (n=360 per study) who were randomized to receive lamotrigine 200, 300, or 400 mg daily or placebo during the 19-week treatment phase, including a 7-week dose-escalation phase and a 12-week, fixed-dose maintenance phase. Placebo produced a pain reduction of -1.6 (0-10) overall and -2.0 for patients who accomplished target dose. 63-70% of placebo-treated patients reported adverse events.

V/s Nabilone

Toth *et al*[48] performed a single-center, randomized, double-blind, placebo-controlled, flexible-dose study on DPN subjects achieving e" 30% pain relief (26/37) who were randomized to either flexible-dose nabilone 1-4 mg/day (n=13) or placebo (n=13) in a further 5-week double-blind treatment period and found that 31% of placebo-treated patients reported global end-point improvement.

V/s Oxcarbazepine

Grosskopf *et al*[49] evaluated the efficacy and safety of oxcarbazepine (1200 mg/day) in their multicentre, double-blind, placebo-controlled, 16-week study of 141 DPN patients who were randomized to oxcarbazepine (1200 mg/day) (n = 71) or placebo (n = 70). The mean reduction in VAS score was similar between the oxcarbazepine and placebo groups.

Dogra *et al*[50] in their multicentre, placebo-controlled, 16-week trial, evaluated the efficacy and safety of oxcarbazepine monotherapy in 146 DPN patients (oxcarbazepine, n=69; placebo, n=77). After 16 weeks, placebo-treated patients also experienced a larger decrease in the average change in VAS score of -14.7 units. At 2nd week, placebo produced a change of -4.7 units on VAS. 18.4% and 22% of Placebo-treated patients experienced a >50% reduction in VAS score and improved Global assessment of therapeutic effect rating at the end of treatment respectively. V/s Oxycodone:

Zin *et al*[51] evaluated the efficacy, safety, and tolerability of pregabalin in combination with oxycodone or placebo in their randomized double-blind, placebo-controlled, parallel-group study of 62 patients with either postherpetic neuralgia (PHN) or painful diabetic neuropathy (PDN) who were randomized to receive either oxycodone mixture 10 mg/day or placebo mixture for 1 week. There were similar levels of overall efficacy found between pregabalin/oxycodone and pregabalin/placebo groups in relieving PHN and PDN related pain.

V/s Ponalrestat

Laudadio and Sima[52] examined the progression rates of quantitative sensory tests, autonomic functions, and sensory and motor nerve electrophysiology in 182 patients designed to placebo treatment in an 18-month multicenter ARI-trial. Clinically meaningful deteriorations were demonstrated in the vibratory perception threshold in the toe and the Valsalva ratio. The greatest deterioration rate in electrophysiologic measures was found in peroneal F-wave latency and in sensory nerve conduction velocities in the upper limb, but none of these reached the threshold of clinically meaningful change.

V/s Pregabalin

Satoh *et al*[53] evaluated the efficacy, safety and pharmacokinetics of pregabalin in theirrandomized, double-blind, placebo-controlled, multicentre 14-week clinical trial on 317 Japanese patients who were randomized to receive placebo or pregabalin at 300 or 600 mg/day and found that 21.5% of placebo-treated patients had >50% reduction in pain post-treatment.

Arezzo *et al*[54] evaluated the efficacy of pregabalin 600 mg/d (300 mg dosed BID)

versus placebo in their randomized, double-blind, placebo-controlled trial, that included 82 patients who received pregabalin and 85 who were given placebo. Placebo-treated patients had higher pain scores than controls. 23% of placebo-treated patients were respnders compared to pregabalin-treated patients (49%), and the former had similar effects on nerve conduction studies (NCS) than the latter.

Richter *et al*[55] in their 6-week, randomized, double-blind, multicenter study evaluated the efficacy of pregabalin on 246 men and women who received pregabalin (150 or 600 mg/day by mouth) or placebo and found that placebo reduced the post-treatment mean pain score to 5.6 and 15% of placebo-treated patients had a > or =50% decrease from baseline pain.

Rosenstock *et al*[56] in their 8-week randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluated the effectiveness of pregabalin on 146 patients who were randomized to receive placebo (n = 70) or pregabalin 300 mg/day (n = 76) and found that Pregabalin produced significant improvements versus placebo for all outcome measures.

V/s Ruboxistaurinmesylate

Vinik *et al*[57] assessed the effects of ruboxistaurin (RBX) mesylate on nerve function and sensory symptoms in patients who were enrolled in a multinational, randomized, Phase II, double-blind, placebo-controlled parallel-group trial comparing 32 mg/d (n=66) or 64 mg/d RBX (n=71) with placebo (n=68) for 1 year. RBX was effective and well tolerated in both doses in the patients with DPN.

Casellini *et al*[58] investigated the effects of the isoform-selective protein kinase-C PKC-beta inhibitor ruboxistaurinmesylate on neurovascular function and other measures of DPN in their double-blind placebo-controlled study that included 20 placebo- and 20 ruboxistaurin-treated (32 mg/day) DPN patients. Placebo group showed 13.1% reduction in Neuropathy total symptom score and 4% in the Norfolk QOL-DN symptom subscore.

V/s Sodium Valproate:

Kochar *et al*[59] tested the effectiveness and safety of sodium valproate in their randomized double-blind placebo-controlled study of 43 DPN patients who were given either drug (group A) or placebo (group B). The placebo group had three dropouts compared to one in drug-treated group, with similar effects on electrophysiological measures tested.

V/s Tapentadol

Schwartz *et al*[60] in their phase III, randomized-withdrawal, placebo-controlled trial evaluated the safety and efficacy of tapentadol extended release (ER) on 588 patientswho were titrated to an optimal dose of tapentadol ER (100-250 mg bid) during a 3-week open-label phaseand 395 patients with at least a 1-point reduction in pain intensity were randomized 1:1 to receive placebo or the optimal fixed dose of tapentadol ER determined during the open-label phase for a 12-week double-blind phase. A total of 60.5% of patients reported at least a 30% improvement in pain intensity in the open-label phase; and 53.6% were responders in the double-blind phase.

V/s Tolrestat

Giugliano *et al*[61] evaluated the effectiveness and safety of tolrestat, an aldose-reductase inhibitor, in their randomized, placebo-controlled, double-blind 52-week trial of 45 patients who were given placebo during a 4-week run-in period (single-blind) followed by random assignment of 20 to continue to receive placebo, and 25 to treatment with tolrestat (200 mg/d given in the morning).The placebo group deteriorated in all test results including VPT except postural hypotension.

V/s Topical basic Fibroblast Growth Factor

Richard *et al*[62] assessed the efficacy and safety of topical human recombinant basic fibroblast growth factor (bFGF) on the healing of diabetic neurotrophic foot ulcers in 17 patients in their a pilot, randomized, double-

blind study comparing of bFGF with placebo. Five out of eight ulcers had healed in placebo group, with equal reduction in ulcer perimeter at the end of the study.

V/s Topiramate

Raskin *et al*[63] in their 12-week multicenter, randomized, double-blind, placebo-controlled trial assessed the topiramate efficacy and tolerability in 323 DPN patients and found that placebo reduced pain score from 69.1 to 54.0 mm;.and 34% of placebo-treated subjects responded to treatment, defined as >30% reduction in pain score.

V/s Tramadol/Acetaminophen

Freeman *et al*[64] examined the efficacy and safety of tramadol/acetaminophen (APAP) by comparing 160 subjects who received tramadol/APAP and 153 who received placebo. Placebo reduced average daily pain from baseline to the final week by -1.83 units.

V/s Venlafaxine

Rowbotham *et al*[65] evaluated the efficacy and safety of 6 weeks of venlafaxine extended-release (ER) (75 mg and 150-225 mg) treatment in their multicenter, double-blind, randomized, placebo-controlled study of 244 outpatients and found that 27% of placebo-treated patients had >50% reduction in pain at 6-weeks, with a post-treatment mean VAS score of 60mm.

V/s Zonisamide

Atli and Dogra[66] analyzed the safety and efficacy of zonisamide in the treatment of painful diabetic neuropathy in their pilot randomized, controlled trial of 25 DPN patients who were randomized to zonisamide (N = 13) or placebo (N = 12). There were no statistically different differences in pain between placebo-treated and drug-treated groups at 6-weeks. More importantly, there were larger dropouts in the latter group compared to the former.

V/s Multiple drugs

V/s Clomipramine or Desipramine

Sindrup *et al*[67] examined the effect of clomipramine and desipramine in their double-blind, randomised, placebo controlled, cross-over study for 2 + 2 + 2 weeks on 19 patients and found that both clomipramine and desipramine significantly reduced the symptoms of neuropathy as measured by observer- and self-rating in comparison with placebo.

V/s Dextromethorphan/Quinidine (DMQ)

Shaibani *et al*[68] evaluated dextromethorphan co-administered with quinidine as treatment of DPNP in their 13-week, phase 3, randomized controlled trial of 379 patients who received double-blind placebo, dextromethorphan/quinidine (DMQ) 45/30 mg, or DMQ 30/30 mg, administered once daily for 7 days and twice daily thereafter. Although therapeutically DMQ was better, the dropouts for adverse events were half in the placebo group compared to the DMQ group.

V/s Ruboxistaurin and Topiramate

Boyd *et al*[69] in their double-blind RCT of 54 DPN patients allocated to treatment on ruboxistaurin (RBX) (n = 18), or topiramate (TPX) (n = 18), or placebo (n = 18). Total QOL scores improved significantly in the active treatment groups but not in placebo.

Discussion

This paper was aimed to evaluate placebo-related responses among patients with DPN who participated in placebo-controlled clinical trials and found that placebo had its powerful positive effects against virtually all drugs given as monotherapy but not so against combination therapies. Similar analysis but on only one study was done by Perkins *et al*[70] on 134 participants who were found to have mild to

moderate DPN with 1-year improvement of 2.0 m/s of summed nerve conduction velocity tests indicating that short-term improvements in glycemic control and serum triglyceride levels have an independent, additive and durable effect on restoration of nerve function.

Drug-specific analyses of clinical trials on neuropathic pain were previously reported for NMDA-receptor antagonists;[71] opioids;[72] gabapentin;[73] pregabalin;[74] duloxetine;[75] and, lamotrigine[12] whereas duloxetine;[76] pregabalin;[77] were reported on people with DPN.

Only few of the included trials operationally defined treatment end-points and treatment-responders through clinically meaningful change in outcomes, and future placebo-controlled trials should address two major types of end points as suggested by Mojaddidi *et al*:[78] "1) those that assess symptoms for defining efficacy in painful diabetic neuropathy, and 2) those that assess neurologic deficits that assess the effects of treatments that may prevent further degeneration or promote repair."

Caution should be exercised prior to inferring conclusions from this review since Luft[79] suggested that the following points be kept in mind when drawing conclusions from the literature: "1) homogeneity of the neuropathy under discussion, 2) severity of the neuropathy, 3) metabolic control, 4) sufficient numbers of probands, 5) sufficient duration of treatment, 6) definition of treatment goals and the impact of surrogate variables, 7) reproducibility of outcome measures, 8) definition of successful treatment, 9) time-dependent changes in both treatment and placebo groups, 10) adequate statistical evaluation, 11) numerical presentation of treatment results, 12) generalization of trial results, 13) tolerable side effects, and 14) publication bias."

Ziegler and Luft[80] opined, "adequate designs for RCTs in diabetic neuropathy must consider the following criteria: type and stage of neuropathy, homogeneity of the study population, outcome measures (neurophysiological markers, intermediate clinical end points, ultimate clinical outcomes, quality of life), natural history, sample size, study duration, reproducibility of neurophysiological and intermediate end points, nonspecific effects of treatment, measures of treatment effect, the extent to which the overall trail result applies to individual patients (external validity), and the reporting of the RCTs."

Although many new therapies were studied in clinical trials, pre-trial testing of underlying pain mechanisms was almost never performed for reasons of cost, risk to subjects, time required, and validation of the techniques used.[81] Also, assessing symptom profiles in neuropathic pain patients could lead to a better understanding which in turn would benefit treatment results.[82]

However, the management of patients with chronic neuropathic pain (NP) is challenging because of the multiplicity of mechanisms involved in NP conditions[83] and hence treating clinicians should effectivély use the power of words and suggestion to involve placebo and to eliminate nocebo in routine practice of people with DPN.[84]

Future placebo-controlled or sham-controlled studies should include placebo/sham interventions in combination with standard care as a comparison group against experimental interventions in addition to standard care along a pragmatic approach to designing, conduct and reporting of clinical trials on DPN.

Conclusion

There was prevalence of treatment-responders in Placebo groups in clinical trials of DPN on drug monotherapy whereas placebo was not effective against combination drug therapy. The study findings suggest an important role of placebo in research and practice of DPN. Evidence for placebo responses for non-pharmacological interventions such as exercise therapy and/or manual therapy was not found.

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