Guideline: use of pharmacological therapy in the treatment of diabetic peripheral neuropathic pain

Nadezhda Ruzhdii

Department of neurology and manual medicine, Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russian Federation

BACKGROUND

Diabetic peripheral neuropathy (DPN) is a prevalent and troublesome complication of diabetes mellitus, often leading to chronic neuropatic pain conditions and disabling with modearate or severe pain for many years and are responsible for considerable loss of quality of life, employment, and increased healthcare costs [1]. Amitriptyline (AMT) had been a first-line treatment for diabetic peripheral neuropathic pain (DPNP) for many years and is still widely used. Currently, the choice of pain therapy is often made by the prescriber based on the own preferences use amitriptilin, gabapentin (GBP), pregabalin (PRG) or duloxetine (DLX).

RESEARCH QUESTIONS

PICO question: wheather pregabalin or gabapentin or duloxetine should be used as first-line treatment instead of standard of treatment (amitriptilin) of diabetic peripheral neuropathic pain.Population: diabetic peripheral neuropatic pain individuals 2) Intervention: pregabalin or gabapentin or duloxetine treatment or standart AMT treatment ; 3) Setting: all countries; 4) Outcome: reduced neuropatic pain. Side symptoms reported in the studies: diarrhoea, dizziness, headache, somnolence and nausea considered as adverse events (AE). Outcomes related to adverse events were rated and considered to be important. Number of deaths was classified as a critical outcome. Guideline development followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group recommendations in population perspective.

IDENTIFICATION OF STUDIES

A comprehensive and systematic search of the published literature for trials of DLX, PGB, GBP and AMT in the treatment of DPNP published in English prior to May 2021 in accordance with the PRISMA statement [9] was performed using Medline (via Pub Med), EMBASE, Cochrane Central Register of Controlled Trials and Database of Systematic Reviews and Scopus databases. We found 63 publications related to our PICO question.

KEY words used for search: “diabetic peripheral neuropathic pain” OR " diabetic neuropathic pain" OR " diabetic peripheral neuropathy" OR " diabetic neuropathy" OR "neuropathic pain" OR " neurological complications of diabetes” OR "long term diabetic neurological complications" AND “pregabalin” OR “gabapentin” OR “amitriptylin” OR “duloxetin” AND "clinical trial" OR “cross-over studies” OR “double-blind methods” OR “placebos” OR “random allocation” OR “single-blind methods" AND "humans".

DATA EXTRACTION AND QUALITY APPRAISAL

Identified references were screened using title, abstract and keywords. 27 trials were suitable for full text reading. Studies were considered potentially eligible for inclusion in the meta-analyses if they were 1) parallel design, double-blind, placebo-controlled trials with random assignment to a amitriptylin (AMT) or duloxetin (DLX) or gabapentin (GBP) or pregabalin (PGB) and placebo, of 2) diabetic peripheral neuropathic pain human patients 3) with a designated trial duration; 4) full paper citations in English; 5) assessed at least one of the outcomes defined in our PICO question. Eligibility was confirmed on review of full publications against the above criteria. Additional study data (including dosage and duration of treatment, sample selection criteria, adverse events (AE) and discontinuations during the double-blind trial) should be available and were rewieved. Summary efficacy and tolerability outcomes were also rewieved. Twenty-one articles were excluded cause of: very significant risk of bias (n=6), indirect or insufficient information (n=9), duplicate data (n=7). Remaining studies identified were included in the relevant meta-analysis. The quality of all included trials was assessed by Cochrane methods, evaluating for random sequence generation (selection bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), blinding of participants and personnel (performance bias), selective reporting (reporting bias) and other bias (publication bias etc).

A meta - analyses were performed to estimate effect sizes for response rate (≥ 50% pain reduction) for each medication compared versus placebo, random-effects (RE) models. Comparisons between drug and placebo were expressed as mean differences (MD) with 95% confidence intervals (*MD* (95% CIs)). Treatment differences between studies were tested using the Mann-Whitney U-test, τ^2 - test were used to assess the study heterogeneity. Superiority tests were performed for the direct comparisons of each active drug with placebo for each outcome, using a one-sided 95% confidence interval (CI). The number needed to treat (NNT) – and the number needed to harm (NNH) for discontinuation due to AEs were calculated. NNH was derived from event probabilities in the control group. The data of clinical outcome and adverse events were pooled separately. An evidence profile was created for each of the four medications individually using the GRADEpro software for clinical domain and adverse events.

From 27 potentially relevant publications, 9 studies with a treatment duration of 5–13 weeks were included in the meta-analysis. The DLX studies included 695 patients on active treatment (AT) and 315 on placebo [4,5,6,8,11]; the GBP studies included 514 patients on AT and 316 on placebo [7,8], the PGB studies included 918 patients on AT and 405 on placebo [2,3,8,11] and AMT 413 patients and 118 for placebo[7,9, 11]. Serious risk of bias in one trial with 215 participants on AMT because of incomplete outcome data (attrition bias) was recognized. For one study 122 patients use DLX very serious bias was classified because of small size. No concerns about the risk of bias for remaining trials. Because they are an antidepressants, the studies of DLX and AMT was included in the meta-analyses if mentioned that participants with not diagnosed depression to avoid biasing estimates of the direct effect of medications on DPNP. This restriction was not applied to GBP and PGB stydies.

IMPLEMENTATION

After releasing this evidence-based guideline, some implementation strategies might be anticipated to promote evidence-based practice: 1) Printed educational materials, including patient versions, and their distribution among healthcare and social care staff, patients and their caregivers, stakeholders and patient organizations. 2) Publication of evidence-based research results and presentation at professional conferences and meetings. 3) Use local opinion leaders to promote to evidence-based guidelines as this increases respect and trust and therefore compliance.4) Educational meetings, including a “diabetes school” for patients and workshops arrangement to improve awareness and adherence to clinical guidelines. 5) Dissemination of information by pharmaceutical companies to promote their products. 6) Analysis of professional behavior with feedback on the results. We recommend to update the guideline in five years.

EVIDENCE PROFILE (GRADEPro)

DLX was statistically significantly more effective than placebo [MD 0.856 (0.628; 1.085), p<0.001, τ^2 =0, NNT =5(3; 7)]. DLX resulted in significantly lower premature discontinuation due to lack of efficacy [MD -0.962 (-1.756; -0.117), p=0.024, τ^2 =0] than placebo. Level of certainty: middle (downgraded due to risk of bias). Premature discontinuation due to AEs was significantly more common for DLX than placebo (NNH = 11 (95% CI: 7; 23)). For the individual tolerability outcomes, DLX gave a significantly higher incidence of dizziness [MD 0.817 (0.378; 1.234), p<0.001, τ^2=0], headache [MD 0.466 (0.090; 0.840), p<0.015, τ^2=0], nausea [MD 1.306 (0.932; 1.647), p<0.028, τ^2= 0.028], and somnolence [MD 1.461 (1.033; 1.800), p<0.001, τ^2=0], than placebo. Level of certainty: middle (downgraded due to risk of bias).

PGB was significantly more effective than placebo [MD 0.831 (0. 514; 1.138), p=0.001, τ^2=0.152, NNT = 5(4; 8)] with lower rate of premature discontinuation due to lack of efficacy [MD 0.721 (-1.197; -0.220), p=0.005, τ^2=0.152]. Level of certainty: middle (downgraded due to risk of bias). Premature discontinuation due to AEs occurred significantly more frequently for PGB than placebo (NNH = 19 (95% CI: 10; 48)). Heterogeneity between PGB studies was observed for efficacy [p=0.001, τ^2=0.152], diarrhea [p=0.131, τ^2=0.131] and dizziness [p=0.024, τ^2=0.124]. PGB showed a significantly higher freqency of dizziness [MD 1.874 (1.309; 2.476), p=0.028, τ^2=0.028] and somnolence [MD 2.070 (1.365; 2.790), p=<0.001, τ^2=0] than placebo. Level of certainty: middle (downgraded due to risk of bias and imprecision).

GBP was significantly more efficient vs placebo [MD 1.474 (0.980; 2.201), p<0.001, τ^2=0], (with high level of certainty). It was not possible to calculate an NNT as binary responder rate data were unavailable. GBP presented significantly lower premature discontinuation due to lack of efficacy [MD -1.016 (-2.756; 0.634), p=0.224, τ^2 =0] than placebo. The frequency of headache [MD 1.147 (-0.018; 2.340), p=0.054, τ^2=0], somnolence [MD 1.582 (0.651; 2.517), p=0.001, τ^2=0] and dizziness [MD 1.817 (0.813; 2.842), p=0.001, τ^2=0] was significantly higher GBP group than placebo. Level of certainty: middle (downgraded due to imprecision).

No significant difference was found between AMT vs placebo [MD 0.393 (-0.565; 1.337), p=0.001, τ^2=0], very low level of certainty (downgrded due to very serious risk of bias). One trial introduced data that AMT dosage 50-75 mg daily was significantly more effective compared with placebo [MD 1.191 (1.017; 2.124) p=0.001, τ^2=0], with an NNT of 5 (4; 9). Middle level of certainty (downgrded due to risk of bias). Discontinuation due to AEs with AMT grater then placebo [MD 1.395 (0.674; 3.120,) p=0.001, τ^2=0] the NNH was 11 (6; 57) – Low certainty (downgraded due to serious risk of bias); No data of estimate of premature discontinuation due to lack of efficacy with AMT was found.

Six serious AE (including one death) occurred in participants treated with AMT, DLX, GBP or PGB but the results for individual treatment arms were not reported. Very low certainty (downgraded due to very serious imprecision).Beneficial side effect of DLX, AMT, PGB, GBP on sleep quality was reported. DLX (60 and 120 mg) compared with placebo worsened sleep through reduced sleep efficiency (SE) (p<0.0001 and p<0.05, respectively) and total sleep time (TST) (p<0.0001 and p<0.05, respectively), increased wake after sleep onset (WASO) (p<0.01). PGB (600 mg), compared with placebo, significantly increased SE and TST and reduced WASO (p<0.01 for all). GBP compared with placebo, significantly increased SE and TST (p<0.0001 and p<0.05, respectively), AMT (25 and 50 mg) had no significant effect on SE and TST but did, at the higher dose (75 mg), reduce WASO (p<0.05). Low certainty (downgrded due to risk of bias and indirectness).

RECOMMENDATIONS

Our meta-analysis suggests a benefit of use GBP, PGB and DLX on reduction diabetic peripheral neuropathic pain rather then AMT with probably existence of beneficial side effects on sleep quality. There are an AEs of use GBP, PGB and DLX were raised, from mild to moderate severity and mainly dizziness and somnolence.We did not find any differences in increased mortality of each of four medication, but conclusions are limited due to a small number of specific research. The safety profile of these medication need to be interpreted with caution because of a limited reporting of safety data. Certainty of the evidence of effects is weak due to limitations in the existing trials (brief duration of the trials; instruments used to assess outcomes in trials which may not be clinically meaningful or sensitive enough to the clinical changes and the exclusion of other important outcomes such as improved patient’s quality of life, caregivers burden, impact of daytime activity and the effectivenes of each treatment arms depending on the age and comorbidities). Despite there is no no systematic reviews (SR) found on how patients value the main outcomes, there is probably no important uncertainty or variability. Also, there are no SR on resource requirements in this population or the impact of these interventions on health equity and cost-effectiveness of the intervention. No SR were conducted about the acceptability of the intervention by stakeholders but it is probably should classified as well accepted and also about feasibility, but the intervention is probably feasible to implement.Since GRADE includes a costing requirement to determine the strength of a recommendation, our decision to propose a conditional recommendation for an intervention.In conclusion, we suggest that use GBP, PGB and DLX instead of AMT on diabetic peripheral neuropathy patients may provide a benefits for reduction of diabetic peripheral neuropathic pain, despite important uncertainties remained.Clinicians should discuss with patients and/or their caregivers that the current evidence suggests that the response to treatment as well as the development of adverse effects may vary and they should monitor treatment-related changings in each of these domains. Patient’s values and preferences as well as cost concerns should also be discussed. The strength of the evidence is weak in four domains and the overall strength of the recommendation is weak.Perhaps when choosing a medication to replace AMT with one of the proposed options, the concomitant need for sleep correction should be considered. It may also be better changing therapy within a group of drugs if there has been some therapeutic response to AMT.The need for further studies of the efficacy, safety and cost-effectiveness of medications in different groups of patients with DPNP by gender, age, comorbidities (including sleep and mood disorders), the severity of neuropathy, the impact on the patients' day activity (taking into account the expected effect of somnolence when taking medications) as well as possibly for different types of diabetes.

Type of recommendation: conditional recommendation for the intervention.

RATE OVERALL QUALITY

Determination of direction and strengths of recommendations was based on the available evidence on the balance between desirable and undesirable effects, the quality of evidence, values and preferences and costs.

PICO question	recommendation
Do the desirable effects of the treatment with GBA, PGB or DLX in patients with diabetic peripheral neuropatic pain outweight the undesirable ones?	probably yes
Strength of recommendation	weak

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