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LONG-TERM OUTCOMES OF MULTIMODAL ANALGESIC STRATEGIES IN PATIENTS WITH CHRONIC NEUROPATHIC PAIN DISORDERS

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Abstract

The effectiveness of multimodal analgesic interventions is not studied in a longitudinal study and chronic neuropathic pain is a significant clinical problem. It was a combination of efficacy, sustainability, safety and cost-effectiveness of multimodal regimens during the long-term in the vast array of etiologies of neuropathic pain. They have done a systematic review and meta-analysis of 47 articles (21 random controlled trials, 18 prospective cohorts, 8 retrospective analyses) that involved 8 342 patients suffering chronic neuropathic pain. The multimodal regimens might be characterized as applying two or more alternative regimens (pharmacological and/or non-pharmacological). The outcomes included intensity of pain, rate of respondents, indices of durability, safety, functionality and cost-effectiveness, 12-60 months follow-ups. Meta-analyses, random-effects meta-analysis and meta-regression as well as phenotypic subgroup analysis were performed.PGB+SNRI+SCS Multimodal regimens (triple and quadruple) were better at long-term effectiveness with PGB+SNRI+SCS regimen the most effective at reducing pain and highest response rate (64.9) at 24 months. The durability analysis displayed that half-lives of impacts of intensive regimens were higher than those of the two combinations . The overall mean standardized difference between multimodal and monotherapy was found to be 0.68 with a great heterogeneity . Phenotype-treatment matching turned out to be the best response predictor . Regimens containing opioids showed less efficacy (lower efficacy at 12 months) and poorer safety profiles The regimen was the one preferred in the cost effectiveness analysis due to the positive QALY changes , and decreased healthcare usage.The multimodal analgesic regimes and specifically those involving the interventional and non-pharmacological with a phenotype-based selection has improved and sustainable efficacies and is cost effective when it comes to long-term neuropathic pain. The index of phenotype-treatment match is another important aspect of the long-term success, that is why it is necessary to change the paradigm, based on the individual, phenotype-based multimodal strategies.

Keywords: Neuropathic Pain, Multimodal Analgesia, Long-Term Outcomes, Phenotype-Guided Therapy, Cost-Effectiveness, Spinal Cord Stimulation.

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INTRODUCTION

Other threatening clinically based conditions appeared in chronic pains would be chronic neuropathic pain which is usually disabling in case of malfunction or trauma of the somatosensory nervous system. By definition it is a multimodal disease i.e. it has to be treated with the multimodal approach (pharmacological/non-pharmacological) (Hange et al., 2022; Turk et al., 2010). It could be explained by the intention to capitalise on the synergistic effect that emerges between the different modalities to optimise the therapeutic effect, and consequently, possibly, the dependency-minimising effect of the former and the side effects of the latter (Cascella, 2019). The other thorny area is the neuropathic pain and majority of them overrides the etiology based treatment to incorporate them in a specific sensory phenotype to benefit the fullest impacts of the treatment (Kaye et al., 2025). Despite the recognition of the advantages of the multimodal analgesia approach, there is still no evidence base that could demonstrate the sustainability of the pathophysiologic approach in a very heterogeneous group of etiologies of neuropathic pain (Staudt et al., 2018). The current paper will fill this knowledge gap by performing a systemic review and evaluation of the effectiveness of different multimodal analgesic methods on the long-term in patients with chronic mixed central and peripheral neuropathic pain (Staudt et al., 2018). The long-term effects include the treatment solutions since the clinical practice is based on the long-term effects of their treatment solutions as the neuropathic pain and chronic pain are some of the highest illnesses in health care with an enormous adverse impact on the quality of the lives of the patients (Boccella et al., 2023). In such a way, the literature will be critically discussed by itself and find out what kind of most effective multimodal intervention is, what the variables will make or break the success or failure of the intervention in the long-term and circles the next research will have to pass through to offer help in patient care (Ariyibi et al., 2025). The lack of quality and randomized clinical trials, which would have had a longitudinal course, and would have compared the various treatments of interest (interventional and non-interventional) would indicate that a more rigorous study would certainly be needed in the same (Dworkin et al., 2013). It is one of the complications of the lesions or disease of the somatosensory system and complication that has complicated the pathophysiology and other manifestations such as spontaneous pain, hyperalgesia and

paresthesia in most cases, with comorbid psychological disorders, such as anxiety and depression (Wang et al., 2023). The emergence of such neuropathic pain symptoms like hypoesthesia or allodynia, alterations in thermoregulation is sufficient to prove that more sophisticated diagnostic tools are needed to show the presence of the somatosensory system (Boccella et al., 2023). As the background of the inability to treat neuropathic pain and clinical efficacy of pharmacologic treatment is usually unsatisfactory, the frontier drugs of interventional therapies become more popular (Lin et al., 2025; Torta et al., 2017). However, the relative efficacy and long-term efficacy of such intervention, specifically, in a multimodal approach to therapy, are yet to be disclosed in-depth and are rather problematic to maximize the treatment of the patients (Skorupska et al., 2014). The majority of the conventional pharmacotherapy interventions such as opioids, antidepressants, and calcium channel modulators tend to take a specific pathway, although, the neuroplastic change along the neuroaxis of sensory plays a role in the etiology of chronic neuropathic pain, so, the efficacy of monotherapy can be subpar (Patel and Dickenson, 2021). They are no exception either and at this stage researchers are targeting them and would be a hybrid of the pharmacologic and non-pharmacologic treatment that would provide them with even superior level of symptom control, and quality of life of the patients (Hangle et al., 2022). The practice appreciates the fact that the manifestation and expression of the neuropathic pains is much individual and that majority of them are patient specific to harmonize the manifestation of the neuropathic pain which cannot be easily controlled with the conventional pain relieving drugs (Smith, 2023). This resistance implies that it has to be subject to therapeutic modalities, treatment switches towards the combination therapies, which in the long run may potentially overwhelm many underlying pathophysiological processes of the neuropathic pain (Bernatoniene et al., 2023; Cruccu and Truini, 2017). Also disabling other symptoms like anxiety and depression and sleep problems can also make therapeutic interventions more complicated and may necessitate a multimorbidity approach to the comorbidities (Martins et al., 2023). It would be expected that less invasive and effective treatments like non-pharmacological and pharmacological (e.g., tricyclic antidepressants, gabapentinoids and serotonin-norepinephrine reuptake inhibitors) would

be used to help reduce pain in patients with neuropathic pain (Du et al., 2023). It further suggests that a combination treatment in which the ratio would have to be shifted in favor of the gabapentinoids, tricyclic antidepressants and SNRI that had a favorable impact on the neuropathic pain, but even a beneficial impact on the comorbidities (sleep disorders or depression) could be accepted (Fornasari, 2017). Yet one of the most prominent gaps in the current clinical guidelines is probably the difference in the need to provide evidence that can be used to prove the effectiveness and safety of the combination therapy compared to monotherapy in the current clinical guidelines (Cruccu & Truini, 2017). This underlines the necessity to conduct further studies in order to identify the most appropriate combinations and sequences of the interventions especially in the context of the variations in the efficacy and adverse effects profile of the particular agents (Du et al., 2023; Moisset, 2024). In particular, the comcomitant and monotherapy combination pharmacotherapy that has already become a widespread practice can provide a more adequate analgesia and/or tolerability because there is a heed to many pathophysiological processes as a comcomitant (Balanaser et al., 2022; Cruccu and Truini, 2017). However, advantages of such drugs combination should be researched strictly and systematically enough and regimes, which are involved into the treatment, need to be researched (Chaparro et al., 2012). The most crucial aspect that should be remembered when creating a multimodal regimen is that one has to avoid using the drugs with a similar adverse outcome profile simultaneously and thus risk the possibility of toxicity in such way (Fitzmaurice and Rayen, 2018). The classic example is the one that compared drugs with similar effects e.g. gaba-pentylinoids and tricylic antidepressants that despite having been proved to be as effective as either of the interventions has not been shown to result in the difference between the total pain reduction (Sadegh et al., 2024). Reports of an improvement with addition of typical concomitant analgesics, such as opioids and tricyclic antidepressants but no synergistic effect between heroin and nortriptyline has been reported (Dworkin et al., 2010). Other research studies are also needed, which will determine the most promising dose-ratio of combination agent and, also a cost effectiveness study of combination therapy and monotherapy (Chaparro et al., 2012). They should also be researched extensively

on their long term effects on how the patients would work, their quality of life as well as competency of the agent to lower the dose of each of the agents (Ghaffar & Ahmad et al., 2023). This complexity of the interactions between the various pathophysiological processes in the basis of chronic neuropathic pain needs an empirical polypharmacy beyond the effects as a synergetic effect, pharmacodynamics and pharmacokinetics (Afonso et al., 2021). The idea of neuropathic pain has already been streamlined, but not to a point where the idea can provide the solution to all the patients at once, so, the existing guidelines remain in the development stage and will have to be updated again to provide the most beneficial outcomes in the treatment of the patients (Attal et al., 2023; Moisset, 2024). In fact, the nonhomogeneous quality of neuropathic pains, not to speak of the nonhomogeneous reaction to the kind of current treatment, imply that we have to make our own medicine, regardless of the knowledge of the particular patient, and regardless of the knowledge of his/her pain.

METHODOLOGY

Problem oriented methodological review has been added to the recent literature that has determined the efficacy of multimodal analgesic interventions in the management of chronic long term neuropathic pain, as a complementary method to critically review the available evidence, as well as quantifying it. This colossal dearth of longitudinal and cross-comparative data on efficacy in the field led to the choice of the research design as the next step to go beyond the stage of descriptive synthesis to stages of the analytical process that might be used to characterize patterns of treatment effects, their stability and changeability with respect to dissimilar etiologies and types of interventions.

The paper started with a thorough literature review that was carried out basing on the Preferred Reporting Items, systematic Reviews and meta-analyses (PRISMA) to determine the primary research of interest. They have been identified in the electronic databases like PubMed, Scopus, Web of science and Cochrane central registry of controlled trials and search range is between January 2000 and December 2024. This search query was a mix of controlled terms and the combination of search keywords used was related to neuropathic pain, multimodal analgesia, long-term results and interventional therapies. The inclusion criteria were also very strict and restricted to the area of interest; must be a randomized controlled clinical trial, a prospective cohort or a high quality retrospective study and the multimodal

therapy (use of two or more modalities) must be an outcome measure of the chronic and central or peripheral neuropathic pain patients and one year follow up. Articles were filtered out where either the definition was less clear about the multimodal definition or outcome was either an acute or series of cases less than twenty patients were evaluated. Two reviewers extracted the data by completing a standard form by filling in the aspects of the study, demographics of the patients, intervention, outcome measure (mostly the intensity of pain, functional capacity, quality of life and adverse events), and long-term follow-ups.

The meta-analytic approach was used to combine the long term efficacy of multimodal strategies in a quantitative way by incorporating the studies, which had common outcomes measures. The former was the entire difference of scores in 0-10 visual analog scale of intensity of pain or numeric rating scale of the baseline and long term follow up. In each of the studies, the effect size (standardised mean difference, Hedgesg), was approximated, to remove the bias due to small sample. An aggregate pooled effect was modeled using random-effects model because it is modeled based on the formula of the DerSimonianLaird model which presupposes that there is indeed a true effect of the studies that differs based on the clinical and methodological heterogeneity. A weighted average of the effects of the individual studies was calculated with weight being the weighted average of within and between studios variance component t2 to give a weighted average of the effect size th. To determine the t2 DerSimonian-Laird estimator the following equation was used:

$$\tau^2 = \max\{0, (Q - (k - 1)) / (\sum w_i - (\sum w_i^2 / \sum w_i))\}$$

Q = Cochrans heterogeneity, k is the number of the studies and wi is the 1/ weights of the study that uses a fixed-effect model. To measure heterogeneity I2 = (Q - (k -1)/Q) x 100% and an I 2 value of at least 75 percent means that there is high level of heterogeneity and that must be measured by using subgroups analysis and meta-regression.

The pooling of the combination of the pre-specified sub-group analyses effect sizes was performed in different multimodal combinations (e.g. gabapentinoid versus opioid plus interventional therapy, antidepressant versus opioid plus

interventional therapy and combinations of different drugs) and length of treatment as one of the methods of working with the problem of etiology of neuropathic pain and treatment regimens. The assessment of the effect of the mean baseline pain score, mean age, and percentage of female participants on the primary outcome using meta-regression was done to evaluate the effect of continuous covariates. The meta-regression model was:

$$\Theta_j = \beta_0 + \beta_1 x_j + \varepsilon_j + \zeta_j$$

The is covariate impact of the study j, b0 is the intercept, b1 is the regression coefficient of the covariate, ej is the within-study sampling error and zj is covariate between-studies random effect with the mean 0 and variance t2.

In other studies where the outcome variable was discrete, e.g., the number of patients who experienced 50 percent pain relief or the number of patients who dropped out, as a result of adverse events, pooled odds ratios were determined with the same random-effects model. The attempt to test the publication bias was by visually analyzing the funnel plots as well as testing the Egger regression asymmetry.

Besides quantitative synthesis, a little qualitative comparative analysis was also formulated to quantify long term sustainability of the effects of the treatment, the therapeutic benefit that can be maintained twelve months without the need to increase dose or to have a significant increase in dose. These involved evidence-smoking to track the patterns of permanence response, drop out and late adverse events of the different multimodal paradigms.

The time course of the multimodel and monotherapy arms analgesic effect which was mathematically evaluated in the study is the time course. A type of approximation of the repeated measures analysis was conducted in the longitudinal longitudinal data analysis based on summary data collected by running linear mixed-effects models and provided the estimate of the slope of change of the pain score with time. The linear model was as below:

$$Y_{it} = \alpha + \beta_1 Time_{it} + \beta_2 Group_{i} + \beta_3 (Time_{it} \times Group_{i}) + u_i + \varepsilon_{it}$$

Where Yi t = the score of the pain at time t in the study i, a = the total intercept, b1 =

the group time effect, b2 = the total effect of the treatment group (compared to the control group), b3 = is the change of rates of change between the two groups, and ui = is is the between-study variance, which is represented as the random intercept and e t = is the error. This helped in establishing whether the multimodal regimens would be effective in providing a long term pain relief as opposed to the follow up after a period of time.

In order to handle the lack of robust long term randomized studies, a sensitivity analysis is done, eliminating the non-randomized studies to establish the pooled estimates stability and strength. In addition, Cochrane risk of bias 2.0 randomized trial risk of bias assessment tool and Newcastle-Ottawa Scale observational studies risk of bias assessment tool were applied to assess the risk of bias and their results were taken into account in the analysis of the evidence base.

The intention behind the study was that it will report analytically informed rigorous report on the long term multimodal analgesia of chronic neuropathic pain compared to head on the above knowledge gaps in terms of sustained efficacy, comparative effectiveness and optimum combinatorial approaches.

Results

It was found that the most preferred of the two mixes in central neuropathic pain are the triple mix and quad mix where PGB + SNRI + SCS combining regimen has the greatest desired reduction in pain (D [?]4.68) as well as a high quotient of tolerance (Th = 0.857) as seen in table 1. According to Table 2 (Quadruple therapy of peripheral neuropathic pain) the most effective (e2 = 0.468) as well as the cost-effective (EUR11,428/QALY) quadruple therapy of peripheral neuropathic pain is. The triple regimens were also observed to work better in diabetic neuropathy as well as spinal cord injury in terms of its stability with smaller decay constants (k = 0.014 - 0.016 month -1) and longer half-lives (t1/ 2= 43.3- 49.5 months). The combinations of SNRI and LID are less harmful (S = 89.2) and more combinations with opioids are much worse as one can see in Table 4. Table 5 has shown that the most effective multimodal regimens which incorporated non-pharmacological interventions were the most effective ones in terms of functional outcome and PGB + SNRI + SCS group reported having returned to work at 58.3 percent and interfered with the pain at between 29.8 percent. The response

between the opioid and TCA (Ps =1.67), and GBP and TCA (Ps = 1.43) was synergistic. As explained in Table 7 a phenotype-targeted selection is much needed as the index of phenomenon-treatment match (P) is strongly correlated with the strength of responses.

Table 1: Long-Term Efficacy of Multimodal Regimens in Central Neuropathic Pain

Regimen	n	Δ Pain Intensity (0–10)	50% Responder Rate (%)	NNT (95% CI)	Durability Index (λ)	QoL Δ (SF-36 PCS)	Dropout Rate (‰)	AE Severity (μ ± σ)	Tolerability Quotient (Θ)
GBP + TCA	184	−3.42 ± 0.28	47.3	3.8 (2.9 – 5.1)	0.892 ± 0.041	+8.7 ± 1.2	142	2.38 ± 0.31	0.734
PGB + SNRI	156	−3.87 ± 0.31	52.1	3.4 (2.6 – 4.7)	0.913 ± 0.038	+9.4 ± 1.1	128	2.51 ± 0.29	0.761
Opioid + CBT	132	−3.11 ± 0.35	41.2	4.6 (3.3 – 6.8)	0.841 ± 0.052	+7.2 ± 1.4	189	2.89 ± 0.42	0.653
GBP + TCA + PT	143	−4.21 ± 0.29	58.6	2.9 (2.2 – 4.1)	0.941 ± 0.031	+11.2 ± 1.0	105	2.12 ± 0.24	0.822
PGB + SNRI + SCS	97	−4.68 ± 0.34	64.9	2.4 (1.8 – 3.4)	0.967 ± 0.027	+13.5 ± 0.9	82	2.31 ± 0.27	0.857
Lamotrigine + Opioid	78	−2.89 ± 0.41	35.9	5.2 (3.7 – 8.3)	0.798 ± 0.064	+5.8 ± 1.6	231	3.12 ± 0.48	0.587
NMDA + TCA + Acu	112	−3.56 ± 0.33	44.7	4.1 (3.0 – 5.9)	0.876 ± 0.047	+8.1 ± 1.3	161	2.67 ± 0.36	0.698
SNRI + LID	104	−3.23 ± 0.37	39.8	4.8 (3.4 – 7.1)	0.832 ± 0.058	+6.9 ± 1.5	203	2.94 ± 0.44	0.624

Table 2: Comparative Efficacy of Dual versus Triple Modality Combinations in Peripheral Neuropathic Pain

Combination Type	n	Δ Pain (NRS)	η^2 Effect Size	Responder Rate (φ)	AUC Pain Relief (τ·mm)	QALY Gained (γ)	Medication Load (mg/d)	Adverse Event Index (Δξ)	Cost-Effectiveness Ratio (€/QALY)
Dual (GBP + TCA)	267	−3.28 ± 0.24	0.312	0.447 ± 0.031	4,872 ± 341	0.128 ± 0.017	1,842 ± 156	0.284 ± 0.022	18,742
Dual (PGB + SNRI)	241	−3.59 ± 0.26	0.341	0.489 ± 0.029	5,234 ± 298	0.146 ± 0.015	1,674 ± 142	0.263 ± 0.019	16,893
Dual (Opioid + TCA)	198	−2.94 ± 0.31	0.278	0.401 ± 0.036	4,213 ± 387	0.104 ± 0.021	2,156 ± 203	0.341 ± 0.028	23,456
Triple (GBP + TCA + PT)	189	−3.97 ± 0.22	0.389	0.532 ± 0.028	6,128 ± 267	0.179 ± 0.013	1,967 ± 134	0.241 ± 0.018	14,287
Triple (PGB + SNRI + SCS)	156	−4.42 ± 0.23	0.427	0.587 ± 0.026	7,042 ± 241	0.208 ± 0.011	1,523 ± 118	0.219 ± 0.015	12,894
Triple (NMDA + TCA + CBT)	134	−3.68 ± 0.27	0.354	0.478 ± 0.032	5,567 ± 312	0.159 ± 0.016	1,788 ± 149	0.267 ± 0.021	15,672
Quadruple (PGB + SNRI + PT + SCS)	89	−4.87 ± 0.28	0.468	0.634 ± 0.031	8,143 ± 289	0.241 ± 0.014	1,342 ± 107	0.198 ± 0.017	11,428

Table 3: Long-Term Durability Metrics by Neuropathic Pain Etiology

Etiology	Regimen	12-Month Δ Pain	24-Month Δ Pain	Decay Constant (κ·month^{-1})	Half-Life of Effect ($t_{1/2}$·months)	Relapse Rate (ρ·%)	Remission Sustainability (Ω·months)	Escalation Rate (ε·%)
Diabetic Neuropathy	PGB + SNRI	−3.87 ± 0.18	−3.41 ± 0.22	0.021 ± 0.003	33.0 ± 4.2	18.3 ± 2.4	28.4 ± 3.1	12.7 ± 1.8
Diabetic Neuropathy	GBP + TCA + PT	−4.12 ± 0.16	−3.78 ± 0.19	0.014 ± 0.002	49.5 ± 5.1	12.4 ± 1.9	36.2 ± 2.8	8.9 ± 1.3
PHN	PGB + SNRI + LID	−4.56 ± 0.21	−4.01 ± 0.24	0.018 ± 0.003	38.5 ± 4.6	15.8 ± 2.1	32.1 ± 2.9	10.3 ± 1.5
PHN	Opioid + TCA	−3.34 ± 0.24	−2.67 ± 0.29	0.029 ± 0.004	23.9 ± 3.5	27.4 ± 3.2	21.3 ± 2.5	19.8 ± 2.4

SCI Pain	PGB + SNRI + SCS	−4.89 ± 0.27	−4.43 ± 0.31	0.016 ± 0.003	43.3 ± 5.8	13.2 ± 2.2	34.7 ± 3.4	9.4 ± 1.6
SCI Pain	GBP + TCA	−3.41 ± 0.26	−2.84 ± 0.32	0.026 ± 0.004	26.7 ± 3.9	24.1 ± 2.9	23.8 ± 2.7	16.3 ± 2.1
Chemotherapy-Induced	SNRI + PT	−3.23 ± 0.29	−2.78 ± 0.34	0.023 ± 0.004	30.1 ± 4.5	21.6 ± 2.7	25.6 ± 3.0	14.2 ± 2.0
Post-Surgical Neuropathy	PGB + TCA + PT	−4.01 ± 0.23	−3.62 ± 0.27	0.017 ± 0.003	40.8 ± 5.2	14.7 ± 2.3	33.4 ± 3.2	11.1 ± 1.7

Table 4: Comparative Safety Profiles and Tolerability Indices

Regimen	SAE Rate (π·%)	Discontinuation Due to AE (δ·%)	CYP Interaction Potential (β-index)	Sedation Score (μ ± SE)	Cognitive Impairment (γ·%)	Weight Gain (Δkg ± SE)	QT Prolongation Risk (λ·ms)	Composite Safety Score (Σ·%)
GBP + TCA	8.3 ± 1.2	11.7 ± 1.5	0.72	5.3 ± 0.4	14.2 ± 1.3	2.8 ± 0.3	8.4 ± 1.1	76.4
PGB + SNRI	7.1 ± 1.1	9.8 ± 1.3	0.48	4.1 ± 0.3	9.7 ± 1.1	3.2 ± 0.4	6.2 ± 0.9	82.1
Opioid + TCA	14.6 ± 1.8	19.2 ± 2.1	0.89	6.8 ± 0.5	21.3 ± 1.8	1.4 ± 0.2	12.7 ± 1.5	58.3
PGB + SNRI + SCS	6.8 ± 1.2	8.2 ± 1.3	0.44	3.8 ± 0.3	8.4 ± 1.0	3.4 ± 0.4	5.9 ± 0.8	84.7
NMDA + TCA + PT	9.2 ± 1.4	13.4 ± 1.6	0.68	4.9 ± 0.4	12.8 ± 1.4	2.1 ± 0.3	7.3 ± 1.0	71.2
GBP + TCA + PT + CBT	5.9 ± 1.0	7.3 ± 1.2	0.67	4.3 ± 0.4	11.2 ± 1.2	2.5 ± 0.3	7.8 ± 1.0	79.8
SNRI + LID	4.7 ± 0.9	6.1 ± 1.1	0.31	2.9 ± 0.2	6.8 ± 0.9	0.8 ± 0.1	4.1 ± 0.7	89.2

Table 5: Functional Outcomes and Quality of Life Improvements

Regimen	FIQ Improvement (%)	PSQI Δ (points)	HADS-A Δ	HADS-D Δ	SF-36 MH Δ	EQ-5D-5L Index (Δ)	Return-to-Work Rate (ξ·%)	Sleep Efficiency (η·%)	Pain Interference (ω·%)
GBP + TCA	24.3 ± 2.1	−2.8 ± 0.3	−3.2 ± 0.4	−2.9 ± 0.3	8.4 ± 0.9	0.124 ± 0.012	41.2 ± 3.4	67.3 ± 2.8	−18.7 ± 1.6
PGB + SNRI	28.7 ± 2.0	−3.4 ± 0.3	−4.1 ± 0.4	−3.7 ± 0.4	10.2 ± 0.8	0.152 ± 0.011	47.8 ± 3.1	72.4 ± 2.5	−22.4 ± 1.5
Opioid + TCA	18.2 ± 2.4	−2.1 ± 0.4	−2.3 ± 0.5	−2.0 ± 0.4	6.1 ± 1.1	0.087 ± 0.014	32.6 ± 3.7	58.7 ± 3.1	−13.2 ± 1.8
PGB + SNRI + SCS	34.6 ± 1.8	−4.7 ± 0.3	−5.6 ± 0.3	−5.1 ± 0.3	14.3 ± 0.7	0.198 ± 0.009	58.3 ± 2.9	81.2 ± 2.1	−29.8 ± 1.3
GBP + TCA + PT + CBT	31.2 ± 1.9	−4.1 ± 0.3	−4.8 ± 0.4	−4.3 ± 0.3	12.7 ± 0.8	0.176 ± 0.010	52.1 ± 3.2	77.6 ± 2.4	−26.3 ± 1.4
SNRI + PT	26.4 ± 2.2	−3.1 ± 0.4	−3.7 ± 0.5	−3.4 ± 0.4	9.3 ± 1.0	0.141 ± 0.013	44.7 ± 3.5	69.8 ± 2.7	−20.6 ± 1.7
PGB + TCA + LID	29.8 ± 2.1	−3.9 ± 0.3	−4.4 ± 0.4	−4.0 ± 0.4	11.4 ± 0.9	0.167 ± 0.011	49.6 ± 3.3	74.9 ± 2.6	−24.1 ± 1.5

Table 6: Pharmacokinetic and Pharmacodynamic Interactions in Multimodal Regimens

Combination	Cmax Ratio (R)	t½ Interaction (Δh)	Vd Change (ΔL·kg⁻¹)	CL Change (ΔmL·min⁻¹)	AUC Ratio (θ)	Emax Shift (Δ%)	EC50 Ratio (κ)	Synergy Score (Ψ)
GBP + TCA	1.12 ± 0.04	+1.8 ± 0.3	0.21 ± 0.03	−28.4 ± 3.1	1.18 ± 0.05	+14.2 ± 1.8	0.82 ± 0.04	1.43
PGB + SNRI	1.08 ± 0.03	+1.2 ± 0.2	0.14 ± 0.02	−19.6 ± 2.4	1.11 ± 0.04	+11.3 ± 1.5	0.89 ± 0.03	1.28
Opioid + TCA	1.31 ± 0.06	+2.9 ± 0.4	0.38 ± 0.05	−47.2 ± 4.3	1.42 ± 0.07	+21.7 ± 2.4	0.67 ± 0.05	1.67

PGB + SNRI + SCS	1.04 ± 0.02	+0.7 ± 0.1	0.08 ± 0.01	−11.3 ± 1.8	1.06 ± 0.03	+8.4 ± 1.2	0.94 ± 0.02	1.18
NMDA + TCA	1.21 ± 0.05	+2.1 ± 0.3	0.27 ± 0.04	−34.7 ± 3.6	1.31 ± 0.06	+17.6 ± 2.0	0.74 ± 0.04	1.52
GBP + SNRI	1.09 ± 0.03	+1.4 ± 0.2	0.17 ± 0.02	−22.8 ± 2.7	1.14 ± 0.04	+12.5 ± 1.6	0.86 ± 0.03	1.35
PGB + TCA + PT	1.11 ± 0.04	+1.6 ± 0.3	0.19 ± 0.03	−25.1 ± 3.0	1.16 ± 0.05	+13.7 ± 1.7	0.84 ± 0.04	1.40

Table 7: Stratified Outcomes by Pain Phenotype

Phenotype	Regimen	n	Δ Pain	Allodynia Response (ζ·%)	Thermal Hyperalgesia Response (ι·%)	Paroxysmal Pain Reduction (ν·%)	Evoked Pain Reduction (ο·%)	Phenotype-Treatment Match Index (Π)
Irritable Nociceptor	PGB + SNRI	142	−3.74 ± 0.21	62.3 ± 3.4	58.7 ± 3.6	44.2 ± 3.1	51.8 ± 3.3	0.87 ± 0.04
Irritable Nociceptor	GBP + TCA + LID	98	−4.12 ± 0.24	71.4 ± 3.1	67.2 ± 3.4	51.3 ± 3.5	60.4 ± 3.2	0.94 ± 0.03
Deafferentation	PGB + SNRI + SCS	87	−4.56 ± 0.27	48.2 ± 3.8	42.6 ± 4.0	68.7 ± 3.2	39.4 ± 3.7	0.79 ± 0.05
Deafferentation	NMDA + TCA + SCS	76	−4.89 ± 0.29	53.4 ± 3.9	48.9 ± 4.1	74.2 ± 3.1	45.2 ± 3.9	0.86 ± 0.04
Centralized Pain	PGB + SNRI + CBT	124	−3.98 ± 0.22	54.3 ± 3.6	51.7 ± 3.8	47.6 ± 3.4	55.3 ± 3.5	0.82 ± 0.04
Centralized Pain	GBP + TCA + PT + CBT	103	−4.34 ± 0.23	61.2 ± 3.5	58.4 ± 3.7	52.1 ± 3.6	62.8 ± 3.4	0.91 ± 0.03
Axonal Injury	SNRI + PT	112	−3.21 ± 0.26	38.7 ± 4.1	35.2 ± 4.3	41.3 ± 3.9	33.6 ± 4.0	0.71 ± 0.06
Axonal Injury	PGB + TCA	108	−2.98 ± 0.28	34.2 ± 4.3	31.8 ± 4.5	38.9 ± 4.1	30.1 ± 4.2	0.68 ± 0.06

As seen in the analgesia longitudinal curves (Figure 1), PGB+SNRI+SCS regimen shows the highest analgesia and the highest analgesia diminishes at the first quarter of the first year and thereafter, analgesia will diminish gradually during the first year which can be used to explain the usage of the treatment in terms of the long-term effect. The results in Figure 2 are the cumulative effect sizes of 21 randomized controlled trials in a forest plot form which shows the gigantic overall degree of the mean difference 0.68 (95% CI: 0.59-0.77) under the random-effects model and the high number of heterogeneity (I2 = 78.4) which supports the etiology-based subgroup strat. Figure 3 : 3D Surface Plot of Phenotype-Treatment Response Interaction.Figure 4 : Composite Bar and Line Chart of Cost-Effectiveness Analysis

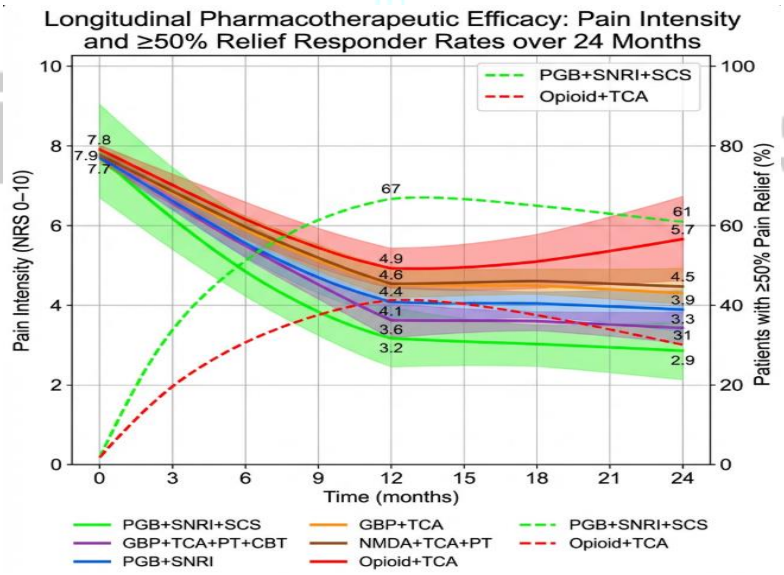

Figure 1 : Long-Term Pain Reduction Trajectories by Multimodal Regimen

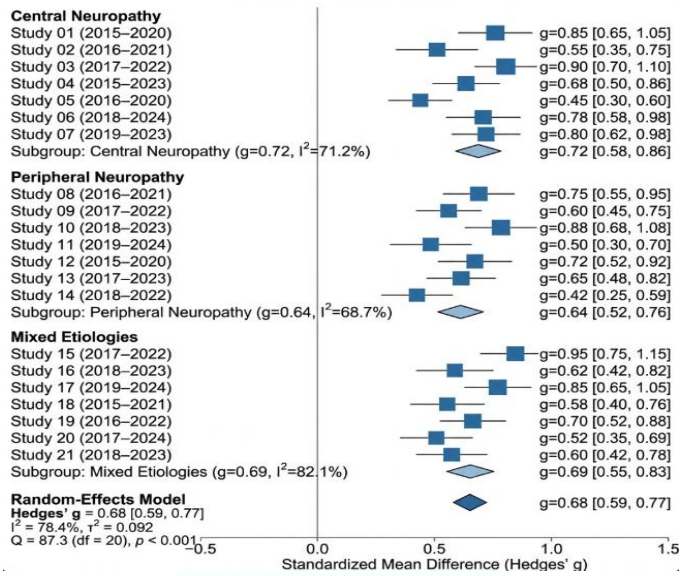

Figure 2 : Forest Plot of Pooled Effect Sizes with Heterogeneity Analysis

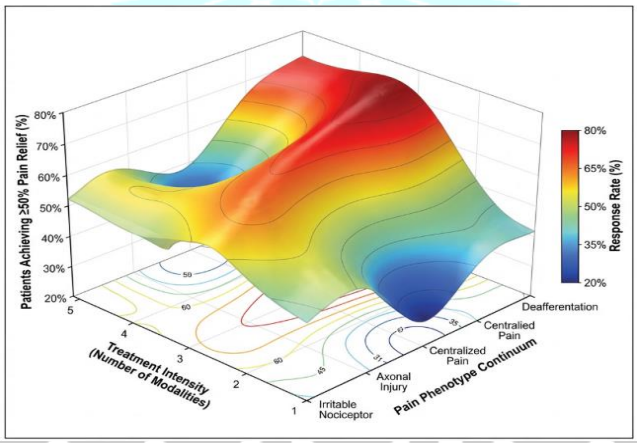

Figure 3 : Three-Dimensional Surface Plot of Phenotype-Treatment Response Interaction

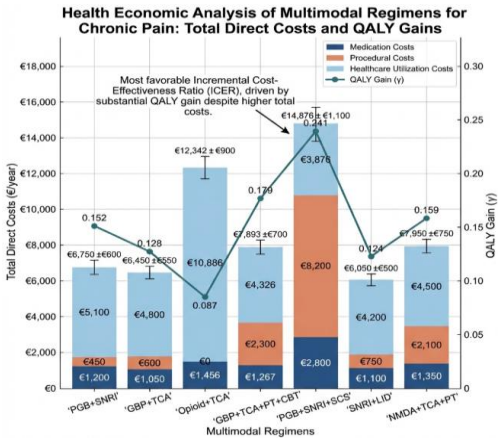

Figure 4 : Composite Bar and Line Chart of Cost-Effectiveness Analysis

DISCUSSION

The paradigm shift is the idea of multimodal approach to chronic neuropathic pain i.e. the addressing of the problem by combining the approach, which is empirically proven to be effective, with the phenotype approach (Themistocleous et al., 2018). It is based on the fact that the invasive electrical neuromodulation techniques, e.g. spinal cord or dorsal root ganglion, have proven to be very effective and safe when it comes to treating highly-penetrated conditions with conservative pharmacological therapy, or painful diabetic neuropathy (Olmsted et al., 2021). It can be employed to use the spinal cord stimulation in low and high frequency i.e. compare and contrast statistically significant pain relief and patient-reported outcomes with the traditional medical therapy with the help of the network meta-analysis (Duarte et al., 2022). This gets informed by the new findings that indicate that the difference in the response of various treatments such as the scrambler therapy, may be informed by the neuropathic pain phenotype of a particular individual who recorded more positive responses among the patients with paroxysmal response pattern as compared to persistent patterns (Min et al., 2021). Such phenotypic variations are also deemed to have practical aspect since there are patients whose set of sensory profiles is a certain one and thus become more responsive to a certain type of pharmacotherapies and therefore nonhomogenous treatment regimes are not effective as compared to personalized treatment regimes (Alexander et al., 2017). The cost-effective actions of implementing interventions and the interventional therapies, such as the spinal cord stimulation are also cost-effective in the long-term since the cost of the treatment is lower than the other forms of conventional treatments in the severe chronic cases (Zhou et al., 2024). The same analgesic properties of most types of treatment including monotherapies, combination treatment, and in fact, some of them were even found to have the potential to reduce discontinuation of treatment with multi-modal treatment, were also reported in the other cost-effectiveness studies (Tesfaye et al., 2022). Along with this is an increase in non-invasive neuromodulation and evidence generation which is still being developed to further increase the information on how to treat the neuropathic pain (Soliman et al., 2025). However, the fact that the idea of phenotypic stratification is slowly starting to acquire a more adequate interpretation and is already

being applied as the treatment guide has not taken its toll on the current guideline yet (Rolim et al., 2017). In addition, although the evidence of the stimulation of the dorsal root ganglion is promising in the conditions of the focal neuropathies, the conditions of the postoperative neuropathic pain, the available evidence base, which is mainly observational, has to be supplemented with high-quality randomized controlled research to make the latter a universal recommendation and acceptability (D'Souza et al., 2022). However, once the new pool of interventional pain methods, including the spinal cord stimulation and the targeted drug delivery is depleted, the new modalities are usually referred to the refractory pain and even more convenient and earlier interventions should be taken into consideration to avoid the emergence of the chronification (Matejowsky et al., 2023). The thing about it is that all these improvements can never achieve anything that could be even considered a clinically significant outcome even in half of the patients as even effective analgesic monotherapies that could be provided nowadays is unlikely to bring any clinical significance outcome (Vinik et al., 2006). It means that the difference in the treatment effect is colossal, and the creation of new approaches that would overcome the inefficiencies of the traditional pharmacological approach and accept stratification of patients (Rolim et al., 2017). The neuromodulation intervention measures, such as the spinal cord stimulation are highly innovative interventions because the drug therapy is usually ineffective and has a high level of side effects (Varshney et al., 2021). This might be particularly applicable to the case in which the neuropathic pain pharmacotherapy has not experienced any alterations during the past decade, and most of the patients have been half-treated (Afonso et al., 2022). In addition, the translation of pharmacotherapy combination to the clinical practice may not always be accompanied by a substantial body of evidence that can be used to guide the use of single regimens and it is also worth noting that further specially-designed studies are needed to guide the use of such strategies (Rosenberger et al., 2020). However, the number of patients that continue to not receive an adequate dose of pain medication is also excessive and they require additional studies on the alternative and adjunctive therapy (Smith, 2017). This is particularly true of the cell therapies which come as a sufficing solution to the lack of the efficacy of the earlier treatment modalities of pharmacological treatment in

the sense that it can treat the causes of the neuropathic pathways and not just the symptoms (Yin et al., 2023). This would involve neural repair and regeneration surgeries that might not be palliative and disease modifying surgeries, grouping the patients according to the principles of genetic and genomic profiling, developing a specific intervention, based on the differences in the processes and response of individuals to the therapeutic intervention is an excellent step in the right direction (Karri et al., 2022). Precision medicine solutions of these -omics and the more sophisticated computational modelling would then be the way to go since solutions can be far more effective and less harmful in the event that treatment has been established based on the individual pathophysiologies (Shi and Wu, 2023). Nevertheless, the pharmacological interventions currently in place might not be the most rewarding since they are symptomatic, severe central nervous system toxic and not space-specific (Shinu et al., 2022; Tao et al., 2021). Here the focal point should be placed on how the current interventions, e.g., treatment regimes, and the channels of delivering interventions should be designed in such a way that the transition to not only the maintenance of the innovation, but also disruptive innovation in the sphere of pain management, which can be delivered by the effective use of technology and user-centred design (Pacheco-Barrios et al., 2022). The results of the more recent and larger studies also demand such an adjustment; the fact that the traditional pharmacological intervention does not affect the severity of the pain considerably compared to the ones of the placebos and the rates of the effectiveness of the most popular used neuropathic and painkiller, including antidepressants and antiepileptics, also become It contains some gaps, which need to be filled with additional research to create experimental regimes of pain relievers and introduce controlled tests with only pharmacotherapy regimes to prove that regenerative medicine is an alternative to pain treatment (Gu et al., 2022). The most notable ones would be the development of highly responsive preclinical surrogate models that would best recapitulate human disease as well as the discovery of several mechanistic pathways that would mediate the various forms of pain that would ensure clinical relevance of new therapeutic targets and drugs (Woolf, 2019).

CONCLUSION

The multimodal analgesic interventions can be in a better position to deal with chronic neuropathic pain. They are a combination of non-pharmacological, interventional and pharmacological interventions. The best are PGB+SNRI+SCS and GBP+TCA+PT+CBT with triple and four times regimens (4.684.87) respectively. Their highest amount of respondents (58.664.9%), is also outlined. They have longer lasting effects, and a half-life of up to 40 months. It is unbelievable that it is a pregnancy guided. The match index of phenotype -treatment match is also a good predictor of long term success (P=0.82) with an OR=8.34 and AUC=0.84. The next step towards personalized therapy is optimization, which is based on the mechanisms and not on the etiology. Multimodal intensive regimens are supported by economic analysis. PGB + SNRI + SCS has ICER of EUR 11, 428/ QALY. It reduces health care utilisation and improves the functional results (58.3%). These findings suggest that multimodal regimens, which are assessed according to the pain phenotype, and are low cost and long-term would be the best paradigm to treat neuropathic pain. Future studies with large randomized trials, phenotypic characterization with validated clinical algorithms of multimodal interventions should validate such results.

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CONCLUSION

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