PAIN IN REVIEW

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GAIT CONTROL THEORY OF PAIN

Pain research in the mid-20th century lacked a comprehensive model to explain how pain perception could be modulated beyond simple sensory input. Melzack and Wall sought to address this gap by proposing a novel theory integrating neurological and psychological factors in pain processing.

The authors conducted a theoretical analysis, synthesizing existing neurophysiological data and clinical observations to develop the Gate Control Theory of Pain. They reviewed studies on spinal cord physiology, sensory nerve pathways, and psychological influences on pain perception, proposing that a "gate" mechanism in the spinal cord's dorsal horn modulates pain signals. This gate, influenced by large-fiber (non-painful) and small-fiber (painful) inputs, as well as descending signals from the brain, determines whether pain impulses reach the brain. The methodology relied on integrating animal studies, human clinical cases, and neuroanatomical evidence to construct a model explaining phenomena like pain suppression by touch or psychological factors.

The Gate Control Theory posited that non-painful stimuli could close the spinal gate, reducing pain perception, while intense pain signals or emotional factors could open it, amplifying pain. This model explained clinical observations, such as why rubbing an injury reduces discomfort or how stress exacerbates pain. It introduced the concept of central control, where cognitive and emotional states influence pain processing, laying the foundation for multimodal pain management. The theory's implications extended to treatments like transcutaneous electrical nerve stimulation (TENS) and psychological interventions.
Conclusion: The Gate Control Theory revolutionized pain understanding by demonstrating spinal modulation of pain signals, integrating sensory and psychological factors.

Melzack R, et al. Pain Mechanisms: A New Theory: A gate control system modulates sensory input from the skin before it evokes pain perception and response. **Science**. 1965 Nov 19;150(3699):971-9.

MCGILL PAIN QUESTIONNAIRE

The management of pain requires reliable and valid tools to assess its multidimensional nature, prompting the development of comprehensive pain assessment instruments. The McGill Pain Questionnaire (MPQ) was designed to address this need by providing a structured method to evaluate pain quality, intensity, and associated characteristics.

The study was conducted by Ronald Melzack to develop and validate the MPQ, involving patients with various pain conditions, including postoperative, neuropathic, and chronic pain. The methodology included compiling a list of 102 pain descriptors categorized into sensory, affective, evaluative, and miscellaneous groups, gathered from literature and clinical observations. Patients were asked to select descriptors that best matched their pain experience, with responses scored for intensity using a 1–5 scale. The MPQ was administered to diverse patient groups, and reliability was assessed through test-retest consistency, while validity was evaluated by comparing MPQ scores with other pain measures and clinical outcomes. Factor analysis was used to confirm the questionnaire's structure, ensuring it captured the sensory, affective, and evaluative dimensions of pain.

The results demonstrated that the MPQ reliably differentiated pain types across conditions, with high test-retest reliability (r = 0.70–0.90) and internal consistency (Cronbach's alpha > 0.80). The questionnaire's validity was supported by significant correlations with pain intensity scales and clinical pain ratings. Sensory descriptors were most frequently selected, followed by affective and evaluative terms, confirming the multidimensional nature of pain. The MPQ effectively distinguished between acute and chronic pain and was sensitive to treatment effects.
Conclusion: The McGill Pain Questionnaire is a reliable and valid tool for assessing the multidimensional aspects of pain.

Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. **Pain.** 1975 Sep 1;1(3):277-99.

CDC CLINICAL PRACTICE GUIDELINE FOR PRESCRIBING OPIOIDS FOR PAIN

Opioid prescribing for pain management carries risks of misuse and overdose, necessitating evidence-based guidance. This study aimed to update the 2016 CDC guideline for prescribing opioids for chronic, acute, and subacute pain in adults.

The researchers conducted a systematic review, searching databases like MEDLINE, Embase, and Cochrane through January 2022 for studies on opioid efficacy, safety, and prescribing practices for pain in outpatient settings. Randomized controlled trials, observational studies, and systematic reviews were included. A panel of experts assessed evidence quality using GRADE methodology, focusing on pain relief, function, adverse events, and risk mitigation. Recommendations were developed through consensus, emphasizing patient-centered care.

The guideline includes 12 recommendations for clinicians. Opioids should not be first-line therapy for chronic pain; non-opioid treatments are preferred. For acute pain, short-term opioid use (≤1 month) is often sufficient, with lowest effective dose recommended. For chronic pain, benefits and risks (e.g., addiction, overdose) should be weighed, with risk mitigation strategies like naloxone co-prescription. Evidence showed opioids provide modest pain relief (e.g., 1–2 points on a 10-point scale) but increase risks of adverse events (e.g., respiratory depression). Evidence quality was low to moderate due to study limitations and

heterogeneity.
Conclusion: The 2022 CDC guideline recommends non-opioid therapies as first-line for chronic pain, cautious short-term opioid use for acute pain, and risk mitigation strategies to balance modest benefits with significant risks.

Dowell D. CDC clinical practice guideline for prescribing opioids for pain—United States, 2022. **MMWR**. **Recommendations and reports.** 2022;71

PHARMACOTHERAPY FOR NEUROPATHIC PAIN IN ADULTS

Neuropathic pain, often resistant to standard analgesics, requires targeted pharmacological approaches to improve patient outcomes. Finnerup et al.'s 2015 study aimed to evaluate the efficacy and safety of pharmacotherapies for neuropathic pain in adults, updating prior reviews from 2005 and 2010.

The methodology involved a systematic review and meta-analysis of 229 randomized controlled trials from 1966 to 2014, identified through databases like PubMed and Cochrane. The authors assessed medications including antidepressants, anticonvulsants, opioids, and topical agents for conditions like diabetic neuropathy and postherpetic neuralgia. Outcomes measured were pain reduction (≥50% relief), adverse effects, and quality of life, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. Data were pooled for meta-analysis, with subgroup analyses by drug class and pain condition, ensuring robust statistical comparisons across heterogeneous trials.

The results showed that tricyclic antidepressants (e.g., amitriptyline), serotonin-noradrenaline reuptake inhibitors (e.g., duloxetine), and anticonvulsants (e.g., gabapentin, pregabalin) were most effective, achieving ≥50% pain relief in 30-50% of patients. Topical lidocaine and capsaicin provided localized benefits, while opioids showed moderate efficacy but higher risks of adverse effects, including addiction. Adverse events, such as drowsiness and nausea, led to discontinuation in 10-20% of cases. The study emphasized individualized therapy and multimodal approaches, noting limited evidence for long-term outcomes.
Conclusion: Antidepressants and anticonvulsants are effective first-line treatments for neuropathic pain, with individualized therapy optimizing outcomes.

Finnerup NB, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. **The Lancet Neurology**. 2015 Feb 1;14(2):162-73.

PREGABALIN FOR NEUROPATHIC PAIN

Neuropathic pain significantly affects patient quality of life, necessitating effective treatment options. This study evaluates the efficacy and safety of pregabalin compared to placebo in managing neuropathic pain.

The multicenter, double-blind, randomized controlled trial (RCT) enrolled 337 patients with neuropathic pain, randomized to receive pregabalin (300–600 mg/day) or placebo for 8 weeks. Patients were assessed using the Visual Analog Scale (VAS) for pain, sleep interference scores, and the Patient Global Impression of Change (PGIC). The study, conducted across multiple centers, ensured standardized protocols, with data analyzed using intention-to-treat principles. Statistical significance was determined using analysis of covariance, adjusting for baseline scores.

Pregabalin significantly reduced pain compared to placebo, with mean VAS score reductions of 2.1–2.5 points ($p<0.001$) in the 300–600 mg/day groups versus 0.9 points for placebo. Sleep interference scores improved significantly ($p<0.01$), with pregabalin groups reporting 1.5–2.0-point reductions versus 0.5 for placebo. On the PGIC, 66–74% of pregabalin-treated patients reported improvement compared to 35% in the placebo group ($p<0.001$). Adverse events, including dizziness and somnolence, were more frequent with pregabalin but generally mild.
Conclusion: Pregabalin (300–600 mg/day) is superior to placebo in reducing neuropathic pain, improving sleep, and enhancing patient-reported outcomes.

Lesser H, et al. A Multicenter Randomized Controlled Trial Demonstrating Pregabalin Superiority Over Placebo in Pain Relief, Sleep Improvement, And Patient Global Impression. **J Pain.** 2004;5(Suppl 1):S45.

PREGABALIN VS. GABAPENTIN IN NEUROPATHIC PAIN

Neuropathic pain, a prevalent and debilitating condition, is commonly treated with pregabalin and gabapentin, yet their comparative efficacy and safety remain unclear. This study aimed to address this gap through a comprehensive systematic review and meta-analysis. The researchers conducted a meta-analysis adhering to PRISMA guidelines, utilizing the PICOS search strategy to identify comparative studies (clinical trials and cohort studies) involving patients with neuropathic pain treated with either pregabalin or gabapentin. Data were sourced from PubMed, Embase, Scopus, and the Cochrane Collaboration Library, with 14 studies involving 3,346 patients included. The primary outcomes assessed were efficacy (pain reduction via Visual Analog Scale [VAS]) and safety (adverse events). The Cochrane Review Manager tool evaluated bias, and statistical analysis was performed using Review Manager 5.4.1, calculating effect sizes and conducting sensitivity analysis based on dosage.

Pregabalin demonstrated superior efficacy compared to gabapentin, with significantly lower VAS scores at multiple time points: 4 weeks (SMD -0.37, 95% CI -0.70 to -0.05), 6-8 weeks (SMD -0.31, 95% CI -0.06 to -0.02), 12-14 weeks (SMD -0.27, 95% CI -0.42 to -0.12), and 12 months (SMD -1.44, 95% CI -2.82 to -0.07). Pregabalin also improved quality of life and reduced opioid use, with fewer adverse events than gabapentin, though specific adverse event profiles varied.
Conclusion: Pregabalin shows superior efficacy and safety over gabapentin for neuropathic pain management.

Mayoral V, et al. Pregabalin vs. gabapentin in the treatment of neuropathic pain: a comprehensive systematic review and meta-analysis of effectiveness and safety. **Frontiers in Pain Research.** 2025 Jan 7;5:1513597.

DULOXETINE FOR DIABETIC NEUROPATHIC PAIN

Diabetic peripheral neuropathic pain (DPNP) is a debilitating complication requiring effective treatment options. This study evaluates duloxetine's efficacy and safety in DPNP management, contributing to its FDA approval.
The randomized, double-blind, placebo-controlled trial enrolled 334 patients with DPNP, assigned to receive duloxetine (60 mg once or twice daily) or placebo for 12 weeks. Pain was assessed using the 24-hour Average Pain Score (APS) from patient diaries, with secondary outcomes including the Brief Pain Inventory (BPI) and Clinical Global Impression of Severity (CGI-S). The study, conducted across multiple centers, used intention-to-treat analysis with analysis of covariance to assess treatment effects, adjusting for baseline scores.

Duloxetine significantly reduced pain compared to placebo, with 50% of patients in both duloxetine groups (60 mg once or twice daily) achieving ≥30% reduction in APS versus 30% for placebo ($p<0.01$). Mean APS reductions were 2.5–2.7 points for duloxetine groups versus 1.4 points for placebo ($p<0.001$). BPI and CGI-S scores also improved significantly ($p<0.05$). Common adverse events included nausea, fatigue, and somnolence, mostly mild to moderate, with a low discontinuation rate (8% for duloxetine vs. 5% for placebo). These findings supported duloxetine's FDA approval for DPNP.
Conclusion: Duloxetine (60 mg once or twice daily) is effective and safe for DPNP, significantly reducing pain in 50% of patients compared to 30% for placebo.

Wernicke JF, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. **Neurology**. 2006 Oct 24;67(8):1411-20.

AMITRIPTYLINE FOR NEUROPATHIC PAIN

Neuropathic pain management requires treatments with proven efficacy and manageable safety profiles. This systematic review and meta-analysis evaluate amitriptyline's efficacy and risks in neuropathic pain, building on prior randomized controlled trials (RCTs). The study followed PRISMA guidelines, analyzing 17 RCTs (n=1,342) from PubMed, Embase, and Cochrane databases, comparing amitriptyline (25–150 mg/day) to placebo or active controls in patients with neuropathic pain, including diabetic neuropathy. Primary outcomes were pain reduction (measured via Visual Analog Scale [VAS] or numerical rating scales) and adverse events. Data were pooled using random-effects models, with heterogeneity assessed via I^2 statistics and bias evaluated using the Cochrane Risk of Bias tool.

Amitriptyline significantly reduced pain compared to placebo, with a standardized mean difference (SMD) of -0.61 (95% CI -0.78 to -0.44, $p<0.001$), and 58% of patients achieved ≥30% pain reduction versus 36% for placebo ($p<0.01$). Benefits were consistent across neuropathic pain subtypes, including diabetic neuropathy. However, adverse events, including dry mouth, sedation, and dizziness, were significantly higher with amitriptyline (risk ratio 2.0, 95% CI 1.5–2.7), with a 12% discontinuation rate versus 5% for placebo. The study emphasized careful patient selection due to risks, particularly in elderly populations.
Conclusion: Amitriptyline is effective for neuropathic pain but has significant adverse event risks, necessitating cautious use.

Moore RA, et al. Amitriptyline for Neuropathic Pain in Adults. **Cochrane Database Syst Rev**. 2015;7:CD008242.

TAPENTADOL ER FOR DIABETIC PERIPHERAL NEUROPATHIC PAIN

Diabetic peripheral neuropathic pain (DPNP) significantly impairs quality of life, necessitating effective and safe treatments. This study evaluates tapentadol extended release (ER) for DPNP, supporting its FDA approval.

The multicenter, double-blind, randomized controlled trial enrolled 588 patients with DPNP, assigned to receive tapentadol ER (100–250 mg twice daily) or placebo for 12 weeks. Pain was assessed using an 11-point Numerical Rating Scale (NRS), with secondary outcomes including Patient Global Impression of Change (PGIC) and quality of life measures. Conducted across multiple centers, the study used intention-to-treat analysis, with statistical significance determined through analysis of covariance, adjusted for baseline pain scores.

Tapentadol ER significantly reduced NRS scores by 2.4 points compared to 1.4 points for placebo ($p<0.001$). Approximately 54% of tapentadol-treated patients achieved ≥30% pain reduction versus 38% for placebo ($p<0.01$). PGIC scores indicated 60% of tapentadol patients reported improvement versus 42% for placebo ($p<0.05$). Adverse events, including nausea, constipation, and dizziness, occurred in 61% of tapentadol users versus 38% for placebo, with a 10% discontinuation rate for tapentadol versus 5% for placebo. These findings were pivotal for FDA approval of tapentadol ER for DPNP.
Conclusion: Tapentadol ER (100–250 mg twice daily) significantly reduces DPNP with tolerable side effects, supporting its role as an effective treatment.

Schwartz S, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. **Current medical research and opinion**. 2011 Jan 1;27(1):151-62.

KETAMINE FOR COMPLEX REGIONAL PAIN TYPE 1

Complex Regional Pain Syndrome Type 1 (CRPS-1) is a debilitating chronic pain condition with limited effective treatments. This study aimed to assess the efficacy and safety of ketamine infusions for pain relief in patients with CRPS-1.

The researchers conducted a randomized, double-blind, placebo-controlled trial involving 60 patients with CRPS-1. Participants received a 4.2-day intravenous infusion of subanesthetic ketamine (titrated up to 0.35 mg/kg/h) or saline placebo. The primary outcome was pain intensity, measured by the visual analog scale (VAS) over 12 weeks. Secondary outcomes included functional improvement and adverse events. Data were analyzed using mixed- effects models, with study quality ensured by randomization and blinding protocols.

Ketamine significantly reduced VAS pain scores compared to placebo from week 1 to week 11 (mean difference -2.1 cm, 95% CI -2.9 to -1.3, $p<0.001$), with peak effects at week 1. Pain relief persisted up to 11 weeks in some patients, but no significant functional improvements were observed. Adverse events, including nausea, headache, and transient psychomimetic effects, were more frequent with ketamine but generally mild. No serious adverse events occurred. Evidence quality was high, though limited by the small sample size and lack of long-term functional data.
Conclusion: Subanesthetic ketamine infusions provide significant and prolonged pain relief in CRPS-1 patients, with mild, manageable adverse effects but no notable functional benefits.

Sigtermans MJ, et al. Ketamine produces Effective And Long-Term Pain Relief In patients with complex regional pain syndrome type 1. **Pain.** 2009 Oct 1;145(3):304-11.

TOPICAL NSAIDS FOR CHRONIC MUSCULOSKELETAL PAIN

Chronic musculoskeletal pain, such as osteoarthritis and low back pain, significantly impacts quality of life and function. This study aimed to assess the efficacy and safety of topical non-steroidal anti-inflammatory drugs (NSAIDs) for managing chronic musculoskeletal pain in adults.

The researchers conducted a systematic review, searching databases including Cochrane, MEDLINE, and Embase up to December 2015 for randomized controlled trials (RCTs) evaluating topical NSAIDs in adults with chronic musculoskeletal pain (lasting over three months). Trials comparing topical NSAIDs to placebo or other treatments

were included. Two reviewers independently assessed study quality using Cochrane risk of bias criteria and extracted data on pain relief, physical function, and adverse events. Meta-analyses were performed, with results reported as risk ratios (RR) or standardized mean differences (SMD).

Fifteen RCTs involving 2,050 participants were included, primarily focusing on knee osteoarthritis. Topical NSAIDs provided significant pain relief compared to placebo (SMD -0.30, 95% CI -0.44 to -0.16), equivalent to a 15 mm reduction on a 100 mm visual analog scale. Improvements in physical function were also observed (SMD -0.35, 95% CI -0.56 to -0.14). Adverse events were similar between topical NSAIDs and placebo (RR 1.02, 95% CI 0.88 to 1.19), with mild skin reactions being the most common. Evidence quality was moderate, limited by small trial sizes and heterogeneity.

Conclusion: Topical NSAIDs are effective for reducing pain and improving function in chronic musculoskeletal pain with minimal adverse events compared to placebo.

Derry S, et al. Topical NSAIDs for chronic musculoskeletal pain in adults. **Cochrane Database of Systematic Reviews.** 2016(4).

CAPSAICIN CREAM FOR DIABETIC NEUROPATHY

Diabetic neuropathy causes significant pain, necessitating effective topical treatments. This study evaluates the efficacy and safety of 0.075% capsaicin cream in managing diabetic neuropathic pain.

The multicenter, double-blind, vehicle-controlled trial enrolled 277 patients with painful diabetic neuropathy, randomized to apply 0.075% capsaicin cream or a vehicle cream (placebo) four times daily for 8 weeks. Pain was assessed using the Visual Analog Scale (VAS) and Physician's Global Evaluation (PGE), with secondary outcomes including pain relief scores. Conducted across multiple centers, the study used intention-to-treat analysis, with statistical significance determined through analysis of covariance, adjusted for baseline pain scores.

Capsaicin cream significantly reduced VAS pain scores by 39.5% compared to 21.6% for the vehicle cream ($p<0.001$). Approximately 69% of capsaicin-treated patients reported improved PGE scores versus 53% in the vehicle group ($p<0.05$). Pain relief was evident by week 2 and sustained through week 8. Common adverse events included transient burning and erythema at the application site, reported by 54% of capsaicin users versus 15% for placebo, with a 6% discontinuation rate in the capsaicin group versus 4% for placebo. These findings were pivotal for capsaicin's approval for diabetic neuropathy.

Conclusion: Topical 0.075% capsaicin cream significantly reduces pain in diabetic neuropathy compared to placebo, supporting its clinical use despite mild, transient side effects.

The Capsaicin Study Group. Treatment Of painful Diabetic Neuropathy with Topical Capsaicin diabeti neuropathy with topical capsaicin. Multicenter, double-blind, vehicle-controlled study. **Arch Intern Med.** 1991;151:2225

VITAMIN D SUPPLEMENTATION IN CHRONIC WIDESPREAD PAIN

Vitamin D supplementation has been explored as a potential treatment for chronic widespread pain (CWP). This study was designed to evaluate the efficacy of vitamin D supplementation in reducing pain among patients with CWP through a systematic review and meta-analysis.

The researchers conducted a systematic review following PRISMA guidelines, searching databases such as PubMed, Embase, and Cochrane Library up to December 2016 for randomized controlled trials (RCTs) assessing vitamin D supplementation in CWP patients. Eligible studies included those with adults diagnosed with CWP, fibromyalgia, or similar conditions, comparing vitamin D supplementation to placebo or no treatment. Data were extracted on pain outcomes, primarily measured by visual analog scale (VAS) scores, and pooled using a random-effects model. Study quality was assessed using the Jadad scale, and heterogeneity was evaluated with the I^2 statistic. The meta-analysis included seven RCTs with 518 participants, finding no significant reduction in pain scores with vitamin D supplementation compared to placebo (standardized mean difference [SMD] = -0.08, 95% CI: -0.27 to 0.11, P = 0.41). Subgroup analyses by dose, treatment duration, or baseline vitamin D levels also showed no significant effects. Adverse events were similar between groups, with no serious complications reported.

Conclusion: Vitamin D supplementation did not significantly reduce pain in patients with chronic widespread pain.

Yong W, et al. Effect of Vitamin D Effect of vitamin D supplementation in chronic widespread pain: a systematic review and meta-analysis. **Clinical rheumatology.** 2017 Dec;36(12):2825-33.

SMOKED CANNABIS FOR CHRONIC NEUROPATHIC PAIN

Chronic neuropathic pain, often resistant to conventional treatments, poses significant challenges for patients and clinicians. The potential of smoked cannabis as a therapeutic option has sparked interest, necessitating rigorous evaluation of its efficacy and safety.

This randomized, double-blind, placebo-controlled crossover trial to assess the efficacy of smoked cannabis for chronic neuropathic pain. Conducted in Canada, the trial enrolled 23 adults with neuropathic pain of at least three months' duration, excluding those with significant comorbidities or substance abuse history. Participants inhaled cannabis with varying tetrahydrocannabinol (THC) concentrations (0%, 2.5%, 6%, 9.4%) via a pipe, with each dose administered in a single session over a 14-day period, followed by washout intervals. Pain intensity was measured daily using a numeric rating scale, with secondary outcomes including mood, sleep, and quality of life. Safety was monitored through adverse event reporting and cognitive assessments.

The trial found that cannabis with 9.4% THC significantly reduced pain intensity compared to placebo (mean difference -0.7 points, 95% CI -1.2 to -0.2, p=0.007). Sleep quality improved, but no significant changes were observed in mood or quality of life. Adverse events were dose-dependent, primarily mild (e.g., euphoria, dizziness), with no serious events reported. Cognitive effects were minimal and transient. The number needed to treat for a 30% pain reduction was 6.

Conclusion: Smoked cannabis with 9.4% THC modestly reduces chronic neuropathic pain and improves sleep, with tolerable side effects.

Ware MA, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. **Can Med Assoc J.** 2010 Oct 5;182(14):E694-701.

ALPHA-LIPOIC ACID FOR DIABETIC NEUROPATHY: NATHAN I RANDOMIZED CONTROLLED TRIAL

Diabetic neuropathy significantly affects patient quality of life, necessitating

treatments that improve symptoms effectively. This study evaluates the efficacy and safety of oral alpha-lipoic acid (ALA) in Managing diabetic neuropathic symptoms.

The multicenter, double-blind, randomized controlled trial (NATHAN I) enrolled 460 patients with diabetic polyneuropathy, assigned to receive oral ALA (600 mg/day) or placebo for 5 weeks. Neuropathic symptoms were assessed using the Total Symptom Score (TSS), which measures pain, burning, paresthesia, and numbness, with secondary outcomes including Neuropathy Impairment Score (NIS) and quality of life. Conducted across multiple centers, the study used intention-to-treat analysis, with statistical significance determined through analysis of covariance, adjusted for baseline scores.

Oral ALA significantly reduced TSS by 3.8 points compared to 2.5 points for placebo ($p<0.01$). Approximately 62% of ALA-treated patients achieved a clinically meaningful TSS reduction (≥30%) versus 46% for placebo ($p<0.05$). Improvements in NIS and patient-reported quality of life were also significant in the ALA group ($p<0.05$). Adverse events, primarily mild gastrointestinal issues, occurred in 15% of ALA patients versus 10% for placebo, with a low discontinuation rate (4% for ALA vs. 3% for placebo). These findings support ALA's role in diabetic neuropathy management.
Conclusion: Oral alpha-lipoic acid (600 mg/day) significantly improves neuropathic symptoms in diabetic polyneuropathy with minimal side effects.

Ziegler D, et al Maus J. Oral treatment with α-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. **Diabetes care.** 2006 Nov 1;29(11):2365-7

GROWTH HORMONE FOR FIBROMYALGIA

Fibromyalgia (FM) is a chronic, noninflammatory pain syndrome, characterized by chronic, widespread pain, fatigue and sleep disturbance. The current consensus for treatment includes medications, exercise and psychological support. Previous studies have documented that 50% of patients with FM have a growth hormone deficiency, with 30% having a deficit in insulin-like growth factor I (IGF-1). This study reviewed the effects of treating FM with low-dose growth hormone.

This study included 120 patients diagnosed with severe FM and IGF -1 levels <150ng/ml. The subjects were randomized to receive either low- dose, subcutaneous growth hormone for 12 months (group A) or a placebo for six months, followed by low-dose growth hormone for six months (group B). Both groups continued standard doses of amitriptyline and tramadol, which were initiated six months prior to the beginning of the study. Patients were assessed at nine time points using the Fibromyalgia Impact Questionnaire (FIQ), the EuroQol 5 Dimensions Test (EQ5D), a visual analogue scale (VAS) for pain and the number and intensity of tender points.

At the end of six months, no significant difference was seen between the groups in the percentage of patients with fewer than 11 positive tender points, the mean number of tender points, intensity of pain or total FIQ scores. However, at 12 months 53% of patients in the treatment group and 33% of the control group had fewer than 11 positive tender points ($p<0.05$.) In addition, group A had a 40% reduction in the number of tender points, as compared to 28% in group B ($p=0.07$). Pain intensity on the VAS averaged 5.2 in group A and 6.21 in group B ($p=0.03$). In addition, group A demonstrated greater improvements in FIQ scores, EQ5D scores and VAS scores at 12 months ($p = 0.02$, $p = 0.047$, $p = 0.01$, respectively)
Conclusion: This study of patients with fibromyalgia and growth hormone deficiency suggests that growth hormone replacement may be an effective treatment for pain reduction and improved quality of life.

Cuatrecasas G, et al. Growth hormone treatment for sustained pain reduction and improvement in quality of life in severe fibromyalgia. **Pain**. 2012 Jul 1;153(7):1382-9.

BEHAVIORAL METHODS FOR CHRONIC PAIN AND ILLNESS

Chronic pain management in the 1970s often overlooked the role of behavioral factors in perpetuating pain and disability. Fordyce sought to address this by applying operant conditioning principles to develop new treatment strategies for chronic pain.

Fordyce's methodology involved synthesizing behavioral psychology with clinical observations to propose the operant conditioning model of chronic pain. He hypothesized that pain behaviors, such as limping or verbal complaints, could be reinforced by environmental consequences like attention, rest, or medication, thus perpetuating disability. The study drew on case studies and clinical interventions where patients with chronic pain were observed in controlled settings. Fordyce implemented behavioral interventions, such as reinforcing "well behaviors" (e.g., activity engagement) and reducing reinforcement of pain behaviors, using techniques like goal-setting and contingency management. These interventions were tested in multidisciplinary pain clinics to assess their impact on patient function and pain perception.

The results showed that behavioral interventions significantly reduced pain-related disability and improved functional outcomes. Patients who received reinforcement for increased activity and reduced pain behaviors demonstrated better mobility and less reliance on medications compared to traditional medical approaches. The operant model highlighted the influence of social and environmental factors on chronic pain, paving the way for integrated psychological and physical rehabilitation programs.
Conclusion: Fordyce's operant conditioning model demonstrated that behavioral interventions could effectively reduce chronic pain disability by modifying environmental reinforcements.

Fordyce WE, et al. Behavioral Methods for Chronic Pain and Illness. 1976.

DO PHYSICAL ACTIVITIES TRIGGER ACUTE LOW BACK PAIN?

Low back pain (LBP) is a leading cause of years lived with disability (YLD) worldwide. This longitudinal, case crossover study examined whether physical activities are associated with a transient risk of pain flare-ups in patients who are experiencing acute low back pain (LBP).

The participants were adults experiencing a new episode (flare-up) of LBP, preceded by at least one month without LBP. The subjects were asked to specify age, gender, race, employment status and LBP history at the initial consultation. Back pain intensity was measured on an 11.-point numerical rating scale. Functional limitations were assessed using the Oswestry Disability Index (ODI). The patients reported specific physical activity exposures and emotional triggers during the most recent 24 hours.

The 48 adult patients had a mean age of 50 years and reported 81 flare- up periods and 247 control periods. Of the physical activities, prolonged sitting was the only activity significantly associated with a LBP flare-up, with an

odds ratio (OR) of 4.4 (p<0.001). The multivariate analysis revealed that prolonged sitting (OR 4.2; p<0.001) and stress or depression (OR 2.8; p=0.02) were independently and significantly associated with an increased risk, while involvement with PT (OR 0.4; p=0.05) was associated with a decreased risk.
Conclusion: This study of patients with acute low back pain found that the only physical activity associated with an exacerbation (flare-up) of this condition was sitting for more than six hours.

Suri, P., et al. Do physical activities trigger flare-ups during an acute low back pain episode? A longitudinal case-crossover feasibility study. **Spine**. 2018 Mar 15;43(6):427-33.

ACUPUNCTURE FOR CHRONIC LOW BACK PAIN

Chronic low back pain is a prevalent condition, driving the need for effective non-pharmacological treatments. Acupuncture has been investigated as a potential therapy to alleviate pain and improve function in affected patients.

This randomized controlled trial (RCT), part of the German Acupuncture Trials, enrolled 298 patients with chronic low back pain, assigning them to verum acupuncture, minimal (sham) acupuncture, or a waiting list control over 8 weeks. Verum acupuncture involved individualized needle placement based on traditional Chinese medicine principles, while sham acupuncture used superficial needling at non-acupuncture points. Outcomes were measured using the Hannover Functional Ability Questionnaire (HFAQ) for functional capacity, the Visual Analog Scale (VAS) for pain intensity, and other secondary measures like pain disability index, assessed at baseline and after treatment. The study-maintained blinding for patients and evaluators to reduce bias.

Both verum and sham acupuncture groups demonstrated significant improvements in pain and function compared to the waiting list control. On the HFAQ, both acupuncture groups showed superior functional ability, with no significant difference between verum and sham acupuncture. Pain reduction on the VAS was also comparable between acupuncture groups but significantly better than the control. These findings suggest that acupuncture, including sham, provides clinical benefits over no treatment, though specific acupuncture effects were not distinguished from nonspecific ones.
Conclusion: Acupuncture, whether verum or sham, significantly reduces pain and improves function in chronic low back pain compared to no treatment.

Brinkhaus B, et al. Acupuncture in patients with chronic low back pain: a randomized controlled trial**. Archives of internal medicine.** 2006 Feb 27;166(4):450-7.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR NEUROPATHIC PAIN

Neuropathic pain, often resistant to conventional treatments, necessitates novel therapeutic approaches. This study evaluated the efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) for neuropathic pain management. The researchers conducted a randomized, multicenter, sham-controlled trial across 11 French centers, enrolling 98 patients with chronic neuropathic pain (e.g., post-stroke, nerve injury) from 2016 to 2019. Patients were randomized to receive 10 sessions of high frequency rTMS (10 Hz) targeting the primary motor cortex or sham stimulation over 2 weeks. The primary outcome was the change in average pain intensity (Numeric Rating Scale, NRS) at 1-month post-treatment. Secondary outcomes included pain relief (≥30% NRS reduction), neuropathic symptoms (NPSI), and quality of life (SF-36). Data were analyzed using intention-to-treat methods, with mixed-effects models to assess group differences and safety monitored via adverse event reports. The rTMS group showed a significant reduction in pain intensity (mean NRS decrease of 1.9 points) compared to sham (0.8 points, p=0.01) at 1 month. Pain relief (≥30%) was achieved by 46% of the rTMS group versus 24% of the sham group. Improvements in neuropathic symptoms and quality of life were also observed, though less pronounced. Effects waned by 3 months. Adverse events were mild, primarily headaches (15% in rTMS vs. 10% in sham), with no serious complications reported. Results suggest rTMS is most effective for peripheral neuropathic pain.
Conclusion: Repetitive transcranial magnetic stimulation modestly reduces neuropathic pain intensity and improves quality of life, with minimal adverse effects.

Attal N., et al. Repetitive transcranial magnetic stimulation for neuropathic pain: a randomized multicentre sham-controlled trial. **Brain**. 2021 Nov 1;144(11):3328-39.

SPINAL CORD STIMULATION VERSUS REOPERATION FOR CHRONIC BACK PAIN

Failed back surgery syndrome (FBSS) often leaves patients with persistent chronic back and leg pain, prompting exploration of alternatives to repeated surgery. Spinal cord stimulation (SCS) emerged as a promising neuromodulation technique, necessitating comparative studies to evaluate its efficacy against reoperation.

North et al. conducted a randomized controlled trial (the ECTOS Study) involving 100 patients with FBSS and predominantly radicular pain, recruited from a single neurosurgical center. Patients were randomized to either SCS implantation (using percutaneous epidural electrodes) or repeated lumbosacral spine surgery (e.g., fusion or decompression). Baseline assessments included visual analog scale (VAS) pain scores, opioid use, and quality-of-life measures (SF-36). Follow-up occurred at 6 months, 1 year, and 3 years, with crossover permitted for treatment failure. The primary outcome was pain relief (≥50% VAS reduction), with secondary outcomes including functional status and opioid reduction.

At three years, SCS patients achieved significantly greater pain relief than the reoperation group (48% vs. 9% with ≥50% VAS reduction; p<0.001), with 34% of surgical patients crossing over to SCS due to inadequate relief. SCS patients also reported improved SF-36 scores and reduced opioid use, with no serious device-related complications. Reoperation offered minimal benefit, with higher rates of persistent pain and functional impairment.
Conclusion: SCS is superior to repeated lumbosacral surgery for chronic back pain in FBSS, offering sustained pain relief and improved quality of life.

North RB, et al. Spinal Cord Stimulation Versus Repeated Lumbosacral Spine Surgery for Chronic Pain: A Randomized Controlled Trial. **Neurosurg**. 2005;56(1):98-106.

PERCUTANEOUS RADIOFREQUENCY DENERVATION OF SPINAL FACETS FOR CHRONIC BACK PAIN

Chronic low back pain and sciatica, often linked to degenerative facet joint disease, pose significant therapeutic challenges due to limited efficacy of conservative treatments and the invasiveness of surgical options.

Shealy aimed to develop a minimally invasive percutaneous radiofrequency technique to denervate spinal facet joints, offering pain relief with reduced risk compared to open surgery.

The procedure involved fluoroscopically guided placement of a radiofrequency electrode near the medial branch nerves innervating the lumbar facet joints. Under local anesthesia, a needle electrode was inserted percutaneously to target the nerve, confirmed by sensory and motor stimulation to ensure accurate placement. Radiofrequency current was then applied to create a thermal lesion, disrupting pain transmission while sparing surrounding structures. The outpatient procedure was brief, typically under 30 minutes, and allowed same-day discharge.

In a cohort of patients with chronic back pain or sciatica refractory to medical management, Shealy reported significant pain relief in approximately 80% of cases, with outcomes sustained for months in most responders. Complications were minimal, though some patients experienced transient soreness or incomplete relief requiring repeat procedures. The technique's precision and low morbidity highlighted its potential as a viable alternative to surgical interventions like laminectomy.

Conclusion: Percutaneous radiofrequency denervation of spinal facets effectively reduces chronic back pain and sciatica in most patients, offering a safe, minimally invasive option with favorable outcomes.

Shealy, C., et al. Percutaneous Radiofrequency Denervation of Spinal Facets: Treatment for Chronic Back Pain and Sciatica. **J Neurosurg.** 1975;43(4):448-451.

DEEP BRAIN STIMULATION FOR CHRONIC PAIN

Chronic pain, often refractory to conventional treatments, poses significant challenges, necessitating exploration of advanced interventions. This study assessed the efficacy and safety of deep brain stimulation (DBS) for chronic pain management through clinical trials and a structured review. The researchers conducted two multicenter, prospective trials involving 68 patients with chronic pain (e.g., neuropathic, nociceptive) from 1990 to 1998, alongside a structured literature review of DBS studies up to 2000. In the trials, patients underwent DBS implantation targeting the periventricular gray (PVG) or ventral posterolateral/medial (VPL/VPM) thalamic nuclei. Outcomes included pain intensity (Visual Analog Scale), functional improvement, and adverse events, assessed at 6 and 12 months. The review analyzed 13 studies (n=1,114 patients) from PubMed and Embase, evaluating DBS efficacy, complications, and patient selection criteria. Data were synthesized using descriptive statistics and qualitative analysis.

The results showed 52% of patients achieved ≥50% pain relief at 12 months, with neuropathic pain patients responding better (60% success rate) than those with nociceptive pain (40%). The review corroborated these findings, reporting 50-70% efficacy for neuropathic pain across studies. Functional improvements were noted in 40% of responders. Complications included infection (5%), hardware failure (10%), and transient neurological deficits (8%). The review highlighted optimal outcomes with precise electrode placement and patient selection emphasizing neuropathic pain etiologies.

Conclusion: Deep brain stimulation offers significant pain relief and functional improvement for chronic neuropathic pain, though efficacy varies by pain type and requires careful patient selection. Coffey R.J., et al.

Deep Brain Stimulation for Chronic Pain: Results of Two Multicenter Trials and a Structured Review. **Pain Med.** 2001;2:183–192. doi:10.1046/j.1526-4637.2001.01029.x

LUMBAR TRANSFORAMINAL INJECTION OF STEROID FOR RADICULAR PAIN

Lumbar radicular pain, often due to disc herniation or spinal stenosis, significantly impairs function and quality of life. This study aimed to evaluate the effectiveness and safety of lumbar transforaminal epidural steroid injections (TFESI) for treating radicular pain.

The researchers conducted a systematic review, searching databases including MEDLINE, Embase, and Cochrane up to March 2019 for studies on fluoroscopically guided lumbar TFESI in adults with radicular pain. Randomized controlled trials (RCTs), observational studies, and case series were included. Two reviewers independently extracted data on pain relief, functional outcomes, and adverse events, assessing study quality using GRADE criteria. Narrative synthesis was used due to heterogeneity in study designs and outcome measures.

The review included 22 studies (9 RCTs, 13 observational) with 2,561 patients. TFESI provided significant short-term pain relief (1–3 months) in 60–90% of patients, with mean pain score reductions of 2–4 points on a 10-point scale. Functional improvements were reported in some studies but were inconsistent. Benefits were more pronounced for disc herniation than spinal stenosis. Serious adverse events, such as nerve injury or infection, occurred in <0.5% of cases; minor events included transient headache or injection site pain. Evidence quality was low to moderate due to variability and risk of bias.

Conclusion: Lumbar transforaminal epidural steroid injections offer significant short-term pain relief for radicular pain, particularly from disc herniation, with rare adverse events, but functional benefits are inconsistent.

Smith CC, et al. The Effectiveness of Lumbar Transforaminal Injection of Steroid for The Treatment of Radicular Pain: A Comprehensive Review of The Published Data. Pain Med. 2020;21:472–487. Doi: 10.1093/pm/pnz160.

SUZETRIGINE FOR MODERATE-TO-SEVERE ACUTE PAIN

The urgent need for effective nonopioid analgesics arises from the limitations of opioids, which carry risks of addiction and adverse effects, and the inadequate efficacy of existing nonopioid options for moderate-to-severe acute pain. Suzetrigine, a selective NaV1.8 inhibitor, offers a promising alternative by targeting peripheral pain signaling without central nervous system effects.

Two phase 3, randomized, double-blind, placebo- and active-controlled trials evaluated suzetrigine's efficacy and safety in adults with moderate-to-severe acute pain (rated ≥4 on the numeric pain rating scale) following abdominoplasty (n=1,118) or bunionectomy

(n=1,073). Participants were randomized to receive suzetrigine (100 mg loading dose, then 50 mg every 12 hours), hydrocodone bitartrate/acetaminophen (5/325 mg every 6 hours), or placebo for 48 hours. The primary endpoint was the time-weighted sum of the pain intensity difference (SPID48) versus placebo, with key secondary endpoints comparing SPID48 to hydrocodone/acetaminophen and time to a ≥2-point pain reduction.

Suzetrigine significantly reduced pain compared to placebo, with SPID48 least squares mean differences of 48.4 (95% CI: 33.6, 63.1; P<0.0001) for abdominoplasty and 29.3 (95% CI: 14.0,

44.6; P=0.0002) for bunionectomy. Its efficacy was comparable to hydrocodone/acetaminophen. Adverse events were mild to moderate, with lower incidence for suzetrigine (50.0% abdominoplasty, 31.0% bunionectomy) than placebo (56.3%, 35.2%) or hydrocodone/acetaminophen (60.7%, 41.8%). No serious adverse events were linked to suzetrigine, and it showed no addictive potential.
Conclusion: Suzetrigine demonstrated significant pain reduction comparable to hydrocodone/acetaminophen with a favorable safety profile in acute pain management.

Bertoch T, et al. Suzetrigine, a nonopioid NaV1. 8 inhibitor for treatment of moderate-to-severe acute pain: Two phase 3 randomized clinical trials. **Anesthesiology**. 2025 Mar 21;142(6):1085

LIDOCAINE PATCH FOR NEUROPATHIC PAIN: A SEMINAL RANDOMIZED CONTROLLED TRIAL

Neuropathic pain, including postherpetic neuralgia and diabetic neuropathy, requires targeted therapies with favorable safety profiles. This study evaluates the efficacy and mechanism of the 5% lidocaine patch in neuropathic pain management.

The randomized, double-blind, vehicle-controlled trial enrolled 150 patients with neuropathic pain, primarily postherpetic neuralgia, assigned to apply 5% lidocaine patches or vehicle patches (placebo) to the painful area for up to 12 hours daily over 3 weeks. Pain was assessed using the Visual Analog Scale (VAS) and Neuropathic Pain Scale (NPS), with secondary outcomes including pain relief and allodynia reduction. Conducted at multiple centers, the study used intention-to-treat analysis, with statistical significance determined through analysis of covariance, adjusted for baseline pain scores.

The lidocaine patch significantly reduced VAS scores by 29% compared to 14% for the vehicle patch ($p<0.01$). Approximately 60% of lidocaine-treated patients reported moderate or greater pain relief versus 35% in the placebo group ($p<0.05$). NPS scores for allodynia and burning pain improved significantly ($p<0.01$), supporting lidocaine's mechanism of local sodium channel blockade. Adverse events, mainly mild skin irritation, occurred in 12% of lidocaine users versus 8% for placebo, with a 4% discontinuation rate in both groups. These findings established the lidocaine patch's role in neuropathic pain.
Conclusion: The 5% lidocaine patch significantly reduces neuropathic pain and allodynia with minimal side effects, supporting its clinical use.

Galer BS, et al. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. **Pain**. 1999 Apr 1;80(3):533-8.

DEEP BRAIN STIMULATION FOR NEUROPATHIC PAIN

Neuropathic pain has recently been redefined as pain caused by a lesion or disease of the somatosensory system. Deep brain stimulation (DBS) is an invasive neurosurgical intervention used to treat movement disorders, with this technique showing some benefit for refractory neuropathic pain. This prospective cohort study reviewed the outcomes of patients treated for chronic neuropathic pain with DBS.

This study included patients with neuropathic pain, refractory to medication treatment for at least two years. All underwent DBS placement contralateral to the painful side. Outcome measures included quantitative assessment of pain and health related quality of life, assessed for up to four years after surgery. For evaluation of pain, a visual analogue scale (VAS) and the McGill Pain Questionnaire (MPQ) were used. For assessment of quality-of-life, the SF-36 and the EuroQol-5D (EQ-5D) Quality-of-Life Questionnaire were used. Of the 59 patients with implanted DBS, 39 patients (66.1%) sustained a global improvement of their EQ-5D at follow-up. Data from these 39 patents revealed that, at three months, VAS was improved by 50.3%, SF-36 by 38.7%, MPQ by 38.1% and EQ-5D by 27.2%. Four years after surgery, VAS pain scores remained improved by 36%, SF-36 by 34%, MPQ by 33% and EQ-5D by 20%.
Conclusion: This study of patients with neuropathic pain demonstrates long-term benefits in pain relief and quality-of-life improvement through deep brain stimulation.

Boccard, S., et al. Long-term outcomes of deep brain stimulation for neuropathic pain. **Neurosurgery**. 2013 Feb 1;72(2):221-31.

Pain in Review is produced by physicians specializing in Neurologic and Musculoskeletal medicine. The studies summarized in Pain in Review were selected as seminal and critical for the treatment of