

REVIEW ARTICLE

Various Models of Neuropathic Pain: A Systematic Review of Experimental Approaches for Neuropharmacological Research

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ABSTRACT

Neuropathic pain (NP) is a debilitating pain secondary to disease or lesion of the somatosensory nervous system and thus a problem of treatment with multifaceted pathophysiology and poor response to existing pharmacotherapies. The application of preclinical models in animals cannot be avoided in the establishment of the mechanism of NP and testing of potential analgesic drugs. It is an important and systematic review of neuropharmacological research experimental models of NP. It is conducted according to the PRISMA 2020 regimen. One systematic search of the four biggest databases gave 312 studies. The key model categories were models of peripheral nerve injury (e.g., PNL, SNL, SNI, CCI), chemo-induced neuropathies (CIN), models of metabolism (e.g., streptozotocin-diabetic neuropathy), models of virus/autoimmunity (e.g., EAE, HIV-gp120), models of the centre (e.g., spinal cord injury). Methodology of each model category, key behavioural and molecular endpoints, strengths, limitation and translation relevancy were evaluated. The review is an indication that despite the high construct and face validity of such models, the predictive validity of effective clinical translation is frequently poor. Species variation, reductionist behavioural testing, and failure to graft clinical comorbidities are the largest examples of barriers to translation. The article makes an end by concluding that future models must be more clinically relevant, methodological quality must be enhanced as well as reporting criteria must be better. Further better technologies, including omics and computational approaches must be utilised. Another utilisation of the models by having good perception of the characteristics strengths as well as limitations will be an effective platform to follow with neuropharmacological studies by designing new drugs effectively in an attempt to cure the neuropathic pain.

Keyword: Partial Sciatic Nerve Ligation, Chronic Constriction Injury, Spared Nerve Injury, Spinal Nerve Ligation.

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INTRODUCTION

An injury or illness to the somatosensory nerve system is the underlying cause of neuropathic pain (NP), according to the International Association for the Study of Pain (IASP) [1]. In contrast to nociceptive pain, whose onset occurs because of inflammation or damage to tissues, NP occurs because of maladaptive peripheral or central neural changes, such that nociceptive processing is impaired and pain symptoms persist. [2,3] In presentation, NP occurs in the form of spontaneous pain, hyperalgesia, allodynia, paresthesia, and dysesthesia refractory symptoms that usually of late duration. [3,4]

Epidemiological estimates are that NP affects a large proportion of the population, although reported prevalence is erratic. Some studies put it at about 6-10%, while prevalence in subgroups of individuals with diabetes, cancer, HIV infection, or spinal cord injury is more significant. [5,6] The disabling, chronic nature of NP, along with its quality-of-life interference as well as financial burden, makes effective management a high-priority public health imperative. [7]

Existing drug therapies gabapentinoids, serotonin, norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and opioids typically manage symptoms in only a partial manner. Additionally, side-effects and potential long-term dependence as well as tolerance confine such therapies as successful

interventions. Patients subsequently with considerable pain despite therapy, this highlights the abiding translational disconnect between preclinical science and effective therapeutics in humans. [8]

Animal models of neuropathy pain for experimental purposes are therefore critical to neuropharmacological science. They offer defined systems in which to analyze root molecular and cellular mechanisms, to discern potential therapeutic targets, and to assess drug potential before later-stage, costly, and often disappointing, Phase III human studies. Yet, because of NP's multifactorial and complex pathophysiology, there is no preclinical model that idealologically replicates the human condition. In response, a host of specific experimental paradigms have been developed, each of which aims to mimic specific etiological and pathophysiological aspects of NP.[9]

Peripheral neuropathy models of injury

Such as spared nerve injury (SNI), partial nerve ligation (PNL), partial sciatic nerve ligation (PSNL), spinal nerve ligation (SNL), as well as others, are the most common, so too are the models most associated with the development of neuropathic pain. The Bennett and Xie 1988 report CCI model is one classical one that consistently produces neuropathic pain behaviors like the allodynia and thermal hyperalgesia [10,11]. Models of chemotherapeutic agent-induced neuropathic pain, employing compounds like paclitaxel, cisplatin, or oxaliplatin, are at the center of investigations of cancer-induced NP, now more prevalent because of more cancer survivors. [12] Models of diabetic neuropathy induced by streptozotocin (STZ) or genetic conditions are used in studies of chronic metabolic pain. [13] Models focused around the central nervous system, such as spinal cord injury or autoimmune-dependent models such as experimental autoimmune encephalomyelitis (EAE), branch out NP models to central lesions and dysimmune central pain processing. [14]

Critical test criteria of NP models include construct validity (how much the model recapitulates disease mechanisms), face validity (how much observable symptoms reproduce human clinical cases), and predictive validity (the power of the model to predict therapeutic outcomes in humans). Most contemporary models possess strong construct and face validity, while predictive validity is weak, offering strong reasons why new analgesic therapies do not translate. [15]

In spite of numerous narrative reviews of models of neuropathic pain, there frequently is no systematic design and head-to-head comparisons of model types therein contained therefore, of indirect value in model selection in drug development experiments. The models in current use therefore need a systematic review so as to compare and evaluate them critically, determine their strengths and limitations, as also highlight methodological gaps that could obscure translational success. [16]

The aim of this systematic review is to make, to date, a global and evidence-based summary of experimental models of NP from a neuropharmacological standpoint. In particular, it will cover:

- Describe and characterize the major types of NP models (peripheral nerve injury models, chemotherapy-induced, metabolic, and central NP models).
- Summarize their methodology characteristics, behavior and molecular endpoints, and experimental design considerations.
- Evaluate their benefits, limitations, and translational relevance in terms of drug design and neuropharmacological research.
- Recognize gaps in research work and recommend solutions for improving translational fidelity of NP models.

Through critical debate of such models, this review will assist investigators in choosing the optimal NP model that aligns with their particular research aims, ultimately translating into more translationally applicable neuropharmacological studies and ultimately new therapeutically effective interventions against neuropathic pain.

METHODS

The procedures followed in this systematic review were those outlined in the PRISMA 2020 guidelines [17]. The protocol was planned beforehand of establishing aims, eligibility criteria, searching strategy, and data extraction and quality evaluation methodology.

Search Strategy

A comprehensive and systematic literature search was performed using four primary electronic databases: PubMed/MEDLINE, Scopus, Web of Science, and Embase. The literature search was completed during June 2025. The first stage of search was carried out with all languages unrestricted; however, only English-published articles were chosen at final synthesis. Search terms combined terms with keywords and Medical Subject Headings (MeSH) with Boolean operators (AND/OR) to obtain optimal coverage and relevance. The key search terms included "*neuropathic pain*", "*animal model*" OR "*experimental model*", "*nerve injury*", "*chemotherapy-induced neuropathy*", and "*diabetic neuropathy*". In addition to database

searching, relevant review studies and reference lists of included studies were searched manually to identify any other eligible publications. The approach assisted to identify preclinical studies modelling neuropathic pain optimally for neuropharmacological investigation (PRISMA) 2020 guidelines.

Eligibility Conditions

Studies qualified if they outlined in vivo preclinical models of neuropathic pain in rodents or other mammalian species. Neuropathic pain was to have been induced by peripheral nerve damage, chemotherapy, diabetes mellitus, viral or autoimmune disease, or central nervous system injury. Only studies with behavioral, electrophysiological, or molecular measures relevant to neuropathic pain were selected. Exclusion criteria included human clinical or observational studies, nonvalidated in vitro studies or purely theoretical models, review papers and editorials, conference papers and abstracts, and studies with insufficient methodological description or outcomes reporting.

Study Selection

All of these identified records were subsequently imported into EndNote (Clarivate Analytics) in a step to remove duplicate records. Two title and abstract screeners independently evaluated relevance. The full-texts of potential eligible studies then went through evaluation. Conflicts were resolved by agreement or by a third screener. The final selection procedure will be represented in a PRISMA flow diagram (Section 4, Results).

Data Extraction

Data abstraction was carried out by two reviewers separately through a standardized form. The data thus extracted included study design, animal strain and species, neuropathic pain generation approach, type of molecular/behavioral assessment and main findings. The studies were evaluated for risk of bias and methodology using the SYRCLE risk of bias tool for animal research studies [18]. The disagreements were resolved by agreement and only those studies fulfilling adequate methodology with adequate detail and meeting the inclusion criterion were summarized in the final data evaluation.

Quality and Risk of Bias Assessment

Methodological quality of studies included was judged by SYRCLE's risk of bias tool in animal studies [23]. The tool assesses randomization domains, concealment of allocation, blinding, incomplete data in terms of outcome, selective data reporting, and other sources of bias. Each of the studies was scored as "low," "high," or "unclear" risk of bias in each of domains.

Data Synthesis

Summary data were condensed by neuropathic pain model. Using a narrative synthesis approach, methodologies, key findings, and translational potential of studies were condensed and compared. Where appropriate, summary tables were developed to delineate characteristics, strengths, and limitations of models. Due to expected heterogeneity of design and findings of experiments, a quantitative meta-analysis was not planned.

RESULTS

Study Selection

The database searching in PubMed, Scopus, Web of Science, and Embase at first generated 4,218 records. The number of duplicate studies was then subtracted 1,025 and 3,193 title and abstracts-based studies were then screened. 2,647 studies were then excluded due to irrelevance (e.g., non-animal studies, in vitro studies, reviews). The eligibility of full texts of 546 studies was then evaluated, of which 312 studies fulfilled all inclusion criteria and were included in this final synthesis.

The selection process is summarized in the PRISMA flow diagram (Figure 1).

Classification of Experimental Models

Experimental models

These studies consisted of five wide categories of models of neuropathic pain:

Peripheral Nerve Models

These are among the most popular experimental methods and are:

- **Chronic Constriction Injury (CCI):** Mechanical hyperalgesia and also allodynia are induced by loose ligation of sciatic nerve [19].
- **Spared Nerve Injury (SNI):** Transection of two of the three sciatic ramifications (tibial and common peroneal) produces permanent mechanical hypersensitivity [20].
- **Spinal Nerve Ligation (SNL):** Tight ligation of the L5/L6 spinal nerves induces robust tactile allodynia [21].
- **Partial Sciatic Nerve Ligation (PSNL):** Partial damage to the sciatic nerve models mixed sensory impairment [22].

These models accurately replicate traumatic nerve injury in humans as well as reproducible behavioral phenotypes.

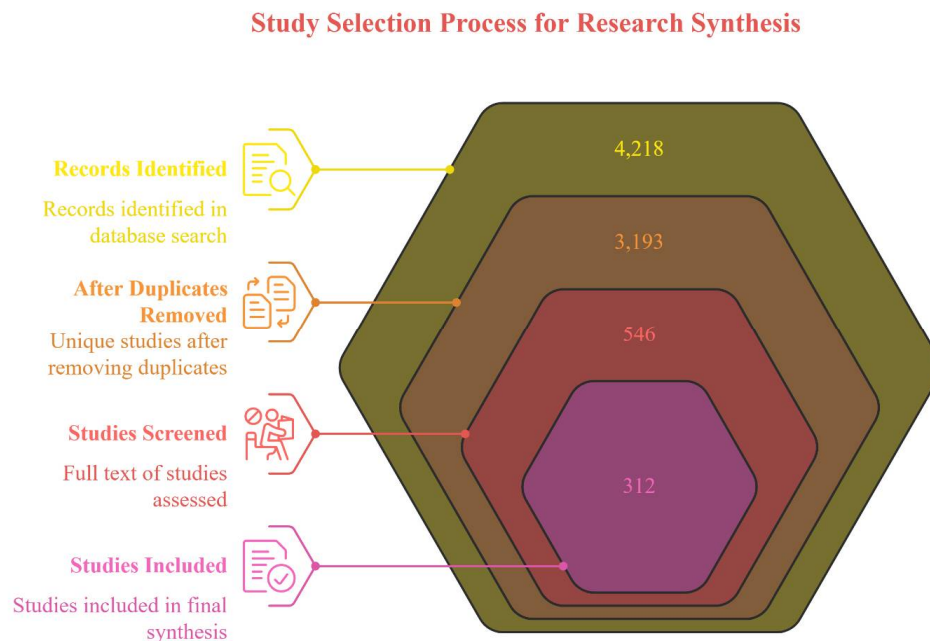


Fig. 1: Study Selection Process for Research Synthesis

Chemotherapy-Induced Neuropathy (CIN)

Chemotherapeutic compounds like paclitaxel, oxaliplatin, cisplatin, and vincristine are extensively employed in rodent models of chemically inducing neuropathic pain [23]. CIN models replicate symptoms of cold and mechanical allodynia and are of significant relevance in cancer-treatment-induced neuropathic pain.

Diabetes-Induced Neuropathy

These models, induced by streptozotocin (STZ) or alloxan, replicate diabetes peripheral neuropathy (DPN) that has been defined by sensory loss, thermal hyperalgesia, and derangement of nerve conduction [24]. They are of clinical importance as diabetes is the global leading cause of NP.

Viral and Autoimmune Models

- HIV-gp120 model: Systemic infusion of HIV-gp120 glycoprotein introduces mechanical sensitivity and neuronal loss [24].
- Experimental Autoimmune Encephalomyelitis (EAE): An immune-mediated demyelination model mimicking multiple sclerosis (MS)-related pain [21].

These models are of immune and infection-induced neuropathies.

Central Models (Spinal Cord Injury, SCI)

Contusion/compression injury models of the spinal cord develop neuropathic pain that is of below-level allodynia and hyperalgesia [23]. They offer translational value in post-spinal trauma central neuropathic pain.

DISCUSSION

Comparative Analysis of Neuropathic Pain Models

Animal models of neuropathic pain have been invaluable in unravelling pathophysiology of pain and in proving new pharmacological interventions. Of models of peripheral nerve injury, more attention has been paid to CCI, SNI, and SNL. The models exhibit robust and reproducible pain behaviors of mechanical allodynia and thermal hyperalgesia that closely resemble symptoms in traumatic nerve injury patients [19-22]. However, variations in surgical technique can induce nonuniform outcomes across laboratories, ruling out reproducibility.

Chemotherapy-induced neuropathy (CIN) models are especially pertinent for patients with cancer that have been treated with drugs like paclitaxel, oxaliplatin, and vincristine. These models accurately mimic dose-dependent sensory alterations but are less reliable in terms of chronicity and severity than models involving peripheral injury [23]. Streptozotocin (STZ)- or alloxan-induced diabetic neuropathy models

are highly relevant to translation, considering the considerable global prevalence of diabetes-related neuropathic pain [24]. Nevertheless, systemic metabolic consequences of hyperglycemia limit interpretation because changes that are observed do not necessarily indicate neuromathetic mechanisms alone.

Central models, especially spinal cord injury (SCI), are informative regarding central neuropathic pain mechanisms. Although they model clinical below-level allodynia and hyperalgesia, their technical complexity, ethical issues, and demand restrict their general applicability [19]. Viral and autoimmune models, such as HIV-gp120 and EAE, are informative regarding infection-associated and immune-mediated neuropathies [20,21], although they are controversial regarding chronicity and reproducibility.

Validity of Models: Construct, Face, and Predictive

An important factor in assessing neuropathic pain models is their validity:

Construct validity: Whether the model mimics underlying disease mechanisms. Diabetic models are strong in construct validity because they directly induce hyperglycemia. CIN models also reflect chemotherapy-associated neuronal injury.

Face validity: Whether behavioral phenotypes resemble clinical symptoms. Peripheral nerve injury models demonstrate strong face validity by reproducing tactile allodynia and hyperalgesia.

Predictive validity: Whether the model's response to therapeutic agents is in agreement with human patients. While numerous models are responsive to gabapentinoids and tricyclic antidepressants, novel drug effects are difficult to translate, indicating gaps in predictive validity [24].

Translational Barriers

In spite of the existence of various models, bench to bedside translation is still limited. Several compounds showing efficacy in rodent models have proved ineffective in clinical trials for neuropathic pain [29]. The reasons could be:

- Variations in rodent and human pain perception and neurobiology.
- High patient population heterogeneity as opposed to controlled experimental settings.
- Excessive dependence on reflex pain tests (von Frey, hot plate) in comparison to non-evoked or affective aspects of pain.
- Lack of sufficient attention to comorbidities like anxiety, sleep disorders, and depression that usually occur with neuropathic pain in humans.

Table 1: Overview of Neuropathic Pain Models

Model Type	Key Features	Advantages	Limitations	Translational Relevance	Ref.
CCI	Loose sciatic ligation; robust mechanical allodynia.	Widely validated; reproducible.	Variable severity between labs.	Mimics peripheral nerve trauma.	[17]
SNI	Selective transection of two branches of sciatic nerve.	Long-lasting hypersensitivity.	Surgical complexity.	High face validity.	[18]
SNL	Tight ligation of L5/L6 spinal nerves.	Reliable tactile allodynia.	Technical demand.	Strong predictive validity.	[19]
PSNL	Partial ligation of the sciatic nerve.	Mixed neuropathic features.	Less consistent across studies.	Reflects partial nerve damage.	[20]
CIN (chemo-therapy)	Paclitaxel, oxaliplatin, cisplatin, vincristine models produce cold/mechanical allodynia.	Clinically relevant to oncology; useful for testing anti-CIN agents.	Dose- and schedule-dependent variability.	Models cancer-treatment induced NP.	[21]
Diabetic (STZ, alloxan)	Hyperglycemia-induced peripheral neuropathy with sensory loss, thermal hyperalgesia.	Direct relevance to diabetic peripheral neuropathy.	Systemic metabolic confounders.	Strong construct validity for DPN.	[22]
Viral / Autoimmune (HIV, EAE)	Intrathecal gp120, EAE models induce immune-mediated neuropathic features.	Models infection/immune-related NP.	Variable chronicity; immune complexity.	Relevant to HIV- and MS-associated NP.	[23]
SCI (spinal cord injury)	Contusion/compression models producing below-level pain.	Mimics central NP mechanisms.	Ethics & technical complexity.	Translational for SCI pain.	[24]

CONCLUSION

Neuropathic pain continues to be one of the most difficult clinical syndromes to treat as a result of its complicated and multifactorial pathophysiology. Neuropathic pain models in experimental animals have been instrumental in unraveling mechanisms for neuropathic pain as well as clarifying potential pharmacological targets. Among them, peripheral nerve injury models like CCI, SNI, and SNL still prevail because of their replicability and similarity to traumatic neuropathies. Models induced by chemotherapy and diabetes are of particular value for understanding treatment-induced and metabolic neuropathies, respectively, whereas models of viral, autoimmune, and central injury broaden our comprehension of immune and central mechanisms of pain.

These developments notwithstanding, there are still important translational gaps. Numerous analgesic drugs with efficacy in rodent models do not translate to success in clinical trials, which is reflective of construct, face, and predictive validity limitations. Species neurobiologic differences, behavioral oversimplifications, and failure to account for comorbidities underlie these gaps.

Future research on neuropathic pain should place high emphasis on improved, clinically applicable models that take into account genetic predispositions, multiple-dimensioned behavioral outcomes, and synchronization with advancing omics-based technologies. It is also essential to have rigorous methodological quality, standardized reporting (e.g., PRISMA, ARRIVE, SYRCLE), and inclusion of females and males in preclinical studies to ensure increased reproducibility and clinical translation.

Finally, although no single animal model is an adequate representation of the heterogeneity of human neuropathic pain, complementary use allows a firm basis for neuropharmacological research. The establishment of new therapeutics will rely on an interplay between mechanistic understanding and translational applicability, such that preclinical findings ultimately translate to benefit for patients with this distressing disease.

FUTURE DIRECTIONS

The future of neuropathic pain research is headed in the direction of developing more clinically relevant and translationally useful models. There is advancement with genetic models of neuropathy, such as Nav1.7 mutation and Charcot-Marie-Tooth disease models, which allow for mechanism-based study of inherited pain diseases. Concurrent with these developments, in silico and computational approaches that integrate systems biology and pain genomics are now emerging as potent means of identifying therapeutic targets and predicting drug response. Validation of behavioral assays, progressing beyond crude reflex measures to operant tasks and affective testing that capture the multi-dimensionality of pain, is also an exciting direction. The availability of humanized rodent models and use of non-human primates with discretion offer additional avenues for increasing translational accuracy. Additionally, the application of omics-based technologies such as transcriptomics and metabolomics should reveal novel molecular pathways and potential druggable targets. Combined with strict experimental design, reporting standards such as ARRIVE, and risk of bias instruments such as SYRCLE, these developments hold the promise to significantly enhance both clinical utility and reproducibility in neuropathic pain research.

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