

INTRODUCTION

- Chronic pain affects approximately 20% of U.S. adults—around 50 million people.¹
- It significantly impacts quality of life and causes an economic burden exceeding \$300 billion annually due to lost productivity.
- Opioids, though commonly used for pain management, have serious drawbacks:
 - Risk of addiction
 - Development of tolerance
 - Limited effectiveness for neuropathic pain
- There is an urgent need for safer and more targeted pain therapies.
- Voltage-gated sodium channels (NaV1.7, NaV1.8, NaV1.9) have been identified as promising targets for selective pain relief.²
- New gene therapy approaches offer potential for long-term solution ³
 - Antisense oligonucleotides (ASOs)
 - CRISPR-based gene editing⁴
 - Optogenetics(uses a combination of genetics and optics to precisely control the activity of specific cells)
- These advances could provide long-lasting or permanent relief by addressing the molecular causes of chronic pain.
- The developments represent a paradigm shift in chronic pain treatment, offering new hope for millions with limited current options.

MATERIALS AND METHODS

- A comprehensive literature review was conducted using the PubMed database.
- The review covered publications from January 2020 through May 2025.
- The search strategy focused on the terms "chronic pain" AND "sodium channels".
- This search initially yielded 259 articles.
- Inclusion criteria included:
 - Observational studies
 - Randomized controlled trials (RCTs)
 - Preclinical and translational research
- After screening, 36 studies were selected for in-depth analysis.
- Multiple reviewers independently performed the screening and selection to minimize bias.
- A thematic analysis was conducted to identify emerging patterns and insights.

SCOPE AND PURPOSE

- This systematic review explores current and emerging therapies targeting voltage-gated sodium channels (VGSCs) for chronic pain treatment.
- Focus areas include:
 - Subtype-selective blockers
 - Gene therapies
 - Nanomedicine-based delivery systems
- Emphasis is placed on selectively inhibiting VGSC subtypes such as:
 - NaV1.7 . NaV1.8 & NaV1.9
- Selective inhibition aims to reduce off-target effects and improve safety compared to traditional, non- selective blockers.
- The review discusses:
 - Gene-editing technologies like CRISPR and antisense oligonucleotides
 - Nanoparticle-based platforms for enhanced tissue targeting and sustained drug release
- Ethical considerations are addressed, including:
 - Long-term effects of genetic manipulation
 - Equitable access to advanced treatments
- The review also examines translational challenges, such as:
 - Moving from preclinical models to human clinical trials
 - The need for rigorous validation, safety assessments, and regulatory oversight

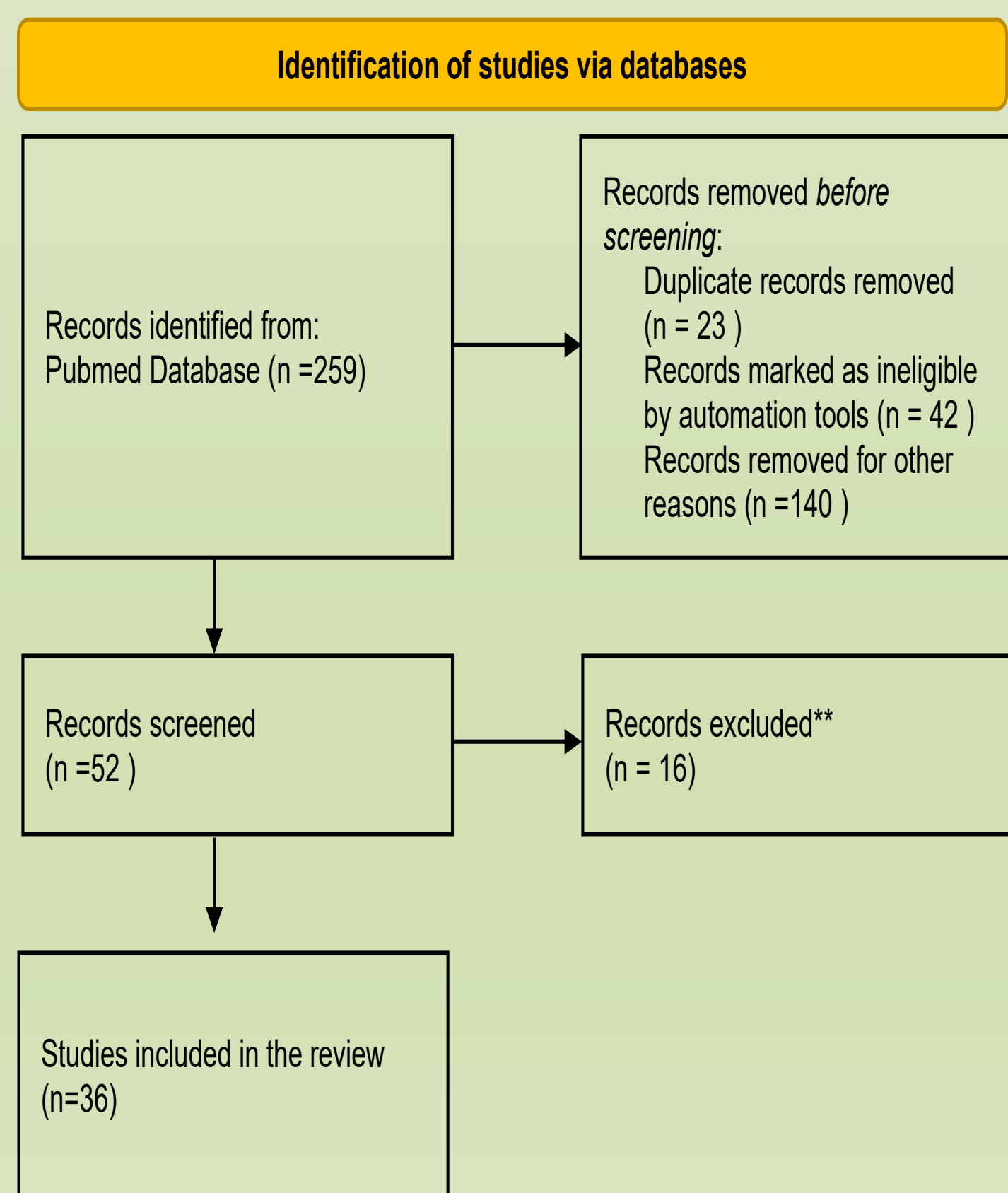


Fig A: Systematic review PRISMA diagram

DISCUSSION

Advancements in NaV-Targeted Pain Therapies

- Recent pain management strategies focus on targeting specific voltage-gated sodium channel (NaV) subtypes for effective, non-addictive analgesia.
- Promising Therapeutic Agents**
 - NaV1.7 inhibitors (e.g., Tsp1a, VX-548):
 - Show promising results in preclinical and early clinical studies.
 - Effective in treating conditions like pelvic pain and irritable bowel syndrome (IBS), where traditional treatments are inadequate.
 - NaV1.8 and NaV1.9 blockers:
 - Agents like Compound 194 and repurposed drugs such as Tramadol show potential for analgesia (Tramadol at higher plasma concentration inhibits NaV1.5 and NaV1.7).
 - Dual-target therapies (e.g., Argentatin C)
 - Provide synergistic pain relief by modulating multiple pathways.
 - Help reduce opioid use and associated adverse effects.

Innovations in Delivery & Gene-Based Approaches

- Drug delivery advancements:
 - Development of brain-penetrant sodium channel blockers.
 - Use of nanomedicine platforms to enhance treatment specificity and overcome biological barriers.
- Gene and epigenetic therapies:⁴
 - Techniques such as CRISPR, antisense oligonucleotides (ASOs), and microRNA modulation⁵ aim to silence or correct pain pathways at the molecular level.

Key Challenges and Considerations

- Ensuring high selectivity to prevent unintended neuronal suppression.
- Addressing long-term safety and ethical concerns, particularly with genetic interventions.
- Overcoming **translational barriers** from animal or computer-generated models to human clinical application.
 - Isoform- selective targeting issues causing off-target and safety concerns
 - Barriers to human translation due to bioavailability and pharmacokinetics
 - Uncertainty regarding sustained therapeutic efficacy with chronic use
 - Regulatory hurdles demanding extensive testing, prolonging approval
 - Unproven long-term safety and tolerability of VGSC-targeted therapies

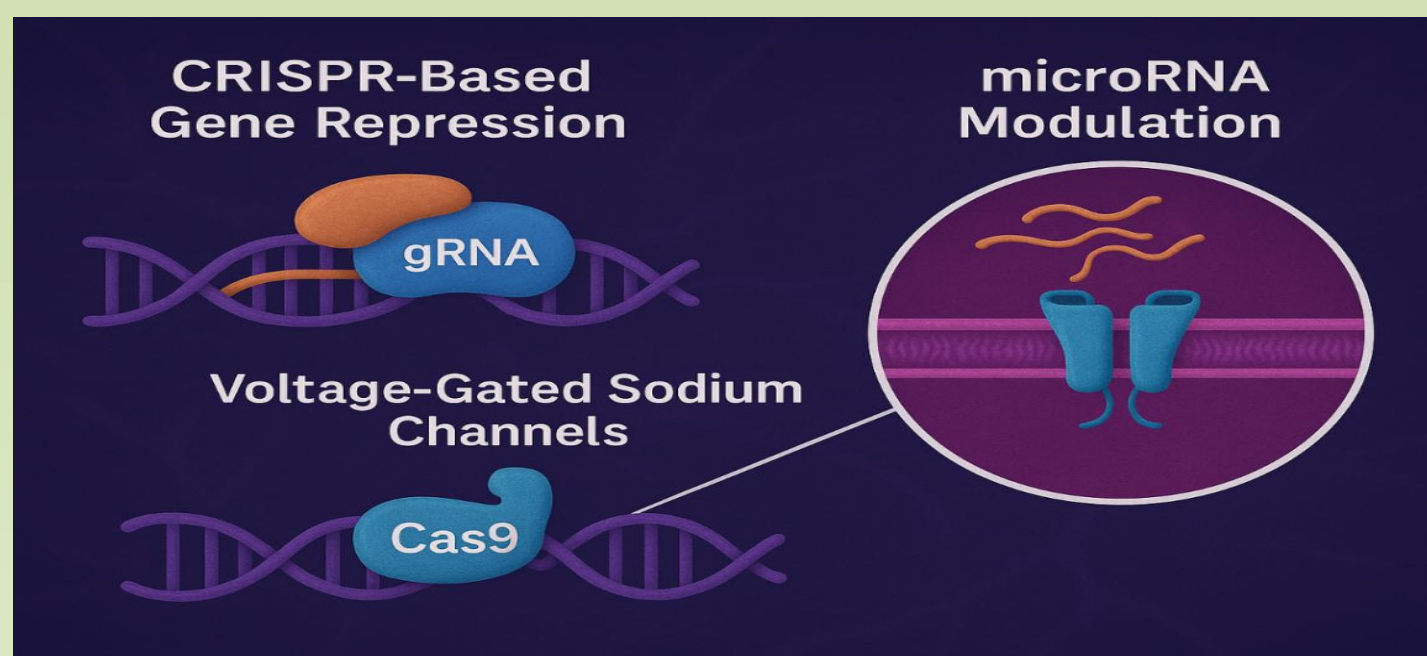


Fig B: CRISPR gene editing

CONCLUSIONS

- NaV1.7, NaV1.8, NaV1.9 = next-generation opioid-sparing targets
- Gene therapies + nanomedicine encouraging in preclinical results
- Barriers: selectivity, drug delivery, long-term safety
- Natural compounds (e.g., quercetin) worth investigating
- Future outlook: sustainable, non-addictive pain relief within reach

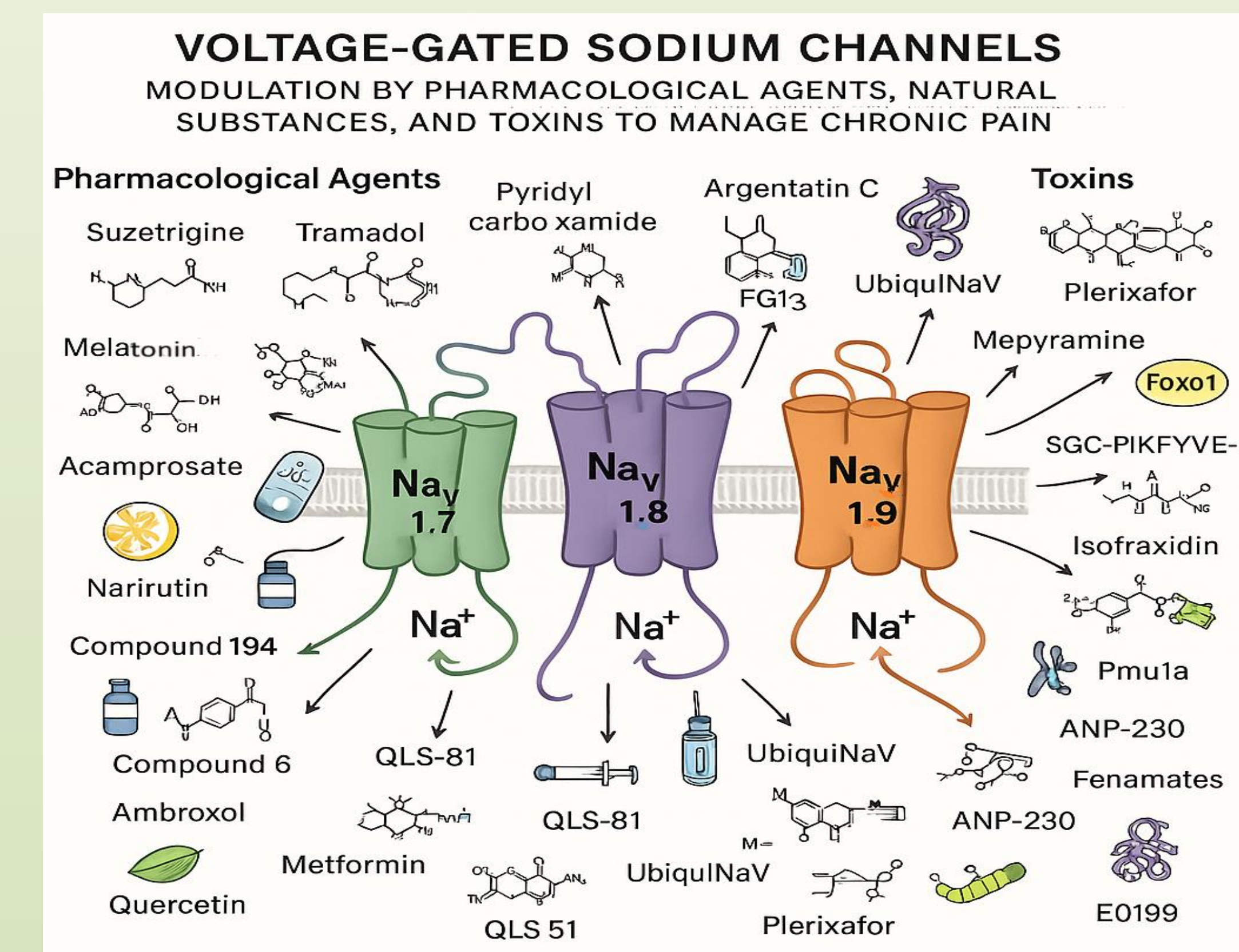


Fig C: Various agents acting on Voltage-gated Na+ channels and their site of action

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