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Assessing the Efficacy of Pain Management Protocols in Rodent Models

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Abstract Effective pain management is crucial for ensuring the welfare of rodents used in biomedical research and maintaining the integrity of scientific outcomes. This study provides an overview of current pain management protocols used in rodent models, focusing on both pharmacological and non-pharmacological approaches. It begins by outlining the anatomical and physiological mechanisms of pain perception in rodents and then discusses common pain assessment techniques. Pharmacological approaches, including opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and local anesthetics, as well as non-pharmacological interventions such as environmental modifications and behavioral interventions, are explored. This study also presents a case demonstrating the application of a novel pain management protocol in a rodent model of neuropathic pain. Despite advancements, challenges remain, including species-specific variability, ethical considerations, and limitations of pain assessment tools. Finally, the study discusses future directions for pain management in rodents, including emerging analgesics, advancements in pain monitoring technologies, and personalized pain management approaches. The findings suggest that optimizing pain control in rodent models can significantly enhance research outcomes and animal welfare.

Keywords Rodent models; Pain management; Pharmacological approaches; Pain assessment; Neuropathic pain

1 Introduction

Pain management in animal research, particularly in rodent models, is a critical aspect of ensuring ethical treatment and maintaining the integrity of scientific outcomes. Despite the ethical imperatives and regulatory requirements to minimize pain, effective pain management protocols are often underutilized in research settings. This underutilization can be attributed to several factors, including insufficient evidence-based data on effective regimens, concerns about the impact of analgesics on study outcomes, and the labor-intensive nature of dosing analgesics at appropriate intervals (Foley et al., 2019). Additionally, there is a misconception that rodents recover quickly from invasive procedures and do not require analgesics, which further complicates the implementation of pain management strategies (Turner et al., 2019).

Effective pain control in rodent models is paramount for several reasons. Firstly, unmanaged pain can significantly affect the welfare of the animals, leading to ethical concerns and potential distress (Otis et al., 2023). Secondly, pain can alter physiological, endocrine, and behavioral responses, thereby impacting the validity and reproducibility of research outcomes (Carbone et al., 2019). Accurate pain assessment and management are essential to mitigate these effects and ensure that the data obtained from rodent models are reliable and translatable to clinical settings. Moreover, the use of validated, non-invasive methods for pain assessment, such as facial grimace scoring and behavioral changes, has shown promise in providing more accurate evaluations of pain in rodents (Domínguez-Oliva et al., 2022).

The primary objective of this systematic study is to assess the efficacy of various pain management protocols in rodent models. This study aims to summarize the current evidence on pharmacological and non-pharmacological strategies for pain mitigation, evaluate the impact of these strategies on animal welfare and research outcomes, and identify gaps in the existing literature that need to be addressed. By providing a comprehensive overview of pain management practices, this study seeks to inform future research and improve the standards of care for rodents in experimental settings.

2 Pain Perception and Mechanisms in Rodents

2.1 Anatomical and physiological basis of pain in rodents

Pain perception in rodents, much like in humans, involves complex interactions between peripheral and central nervous systems. The primary sensory neurons, located in the dorsal root ganglia, detect noxious stimuli and transmit signals to the spinal cord and brain. These neurons express various ion channels and receptors that are crucial for the initiation and modulation of pain signals (Tappe-Theodor et al., 2019). The spinal mechanisms, including synaptic plasticity and neurotransmitter release, play a significant role in the development of hyperexcitability and chronic pain states. Additionally, the anatomical and physiological similarities between rodents and humans, such as the distribution of nociceptive fibers and the structure of the epidermal-dermal junction, make rodents suitable models for studying pain mechanisms (Deuis et al., 2017).

2.2 Types of pain commonly studied in rodent models

Rodent models are extensively used to study various types of pain, including inflammatory, neuropathic, and osteoarthritis pain. Neuropathic pain models often involve nerve injury, such as sciatic nerve ligation, to induce pain-like states and study the resulting behaviors and underlying mechanisms. Osteoarthritis pain models, like the MI-RAT model, combine surgical induction of joint instability with calibrated exercise to mimic the clinical condition and assess sensory sensitivity and joint structural changes (Cunha et al., 2020). Chronic pain models also explore the impact of pain on behavior, including anxiety, depression, and cognitive deficits, which are relevant to the human experience of chronic pain.

2.3 Pain assessment techniques in rodent models

Accurate pain assessment in rodents is critical for evaluating the efficacy of pain management protocols. Traditional methods include stimulus-evoked tests such as the von Frey and Hargreaves tests, which measure withdrawal responses to mechanical or thermal stimuli (Gigliuto et al., 2014). However, these methods may not fully capture the complexity of pain, particularly spontaneous pain and its impact on behavior. Newer techniques focus on non-stimulus-evoked behaviors, such as the Grimace Scale, which assesses facial expressions indicative of pain, and burrowing and nesting activities, which reflect changes in natural behaviors. These methods provide a more comprehensive assessment of pain and its effects on the overall well-being of the animal. Additionally, the use of multiple assessment methods is recommended to improve pain detection and treatment outcomes. By integrating these diverse pain assessment techniques, researchers can better understand the mechanisms of pain and develop more effective pain management strategies for both preclinical and clinical applications (Bouali-Benazzouz et al., 2021).

3 Pain Management Protocols

3.1 Pharmacological approaches

Opioids are commonly used for pain management in rodent models due to their potent analgesic effects. Studies have shown that opioids like buprenorphine are frequently administered to laboratory rodents undergoing surgical procedures. The use of buprenorphine increased from 78% in 2000-2001 to 35% in 2005-2006, indicating a shift towards more refined analgesic practices (Liles and Flecknell, 1992). Additionally, opioids have been found to have minimal impact on fracture healing in orthopedic models, making them suitable for managing pain in such contexts (Costa et al., 2016).

NSAIDs are another class of analgesics widely used in rodent models. They are particularly effective in managing inflammatory pain. Studies have demonstrated the efficacy of NSAIDs like diclofenac and etoricoxib in reducing pain symptoms in various models, including osteoarthritis. However, the use of NSAIDs must be carefully managed due to potential ulcerogenic side effects. In orthopedic and wound healing models, COX2 selective NSAIDs are recommended for short-term use to minimize their impact on healing processes.

Local anesthetics are often used to provide targeted pain relief during and after surgical procedures. Their use has been reported to increase over the years, with a notable rise in the administration of local anesthetics like lidocaine and bupivacaine in recent studies9. Local anesthetics are particularly beneficial in minimizing systemic side effects and providing effective pain relief at the surgical site (Costa et al, 2017).

3.2 Non-pharmacological approaches

Environmental modifications can play a significant role in pain management for rodents. Adjustments such as providing soft bedding, nesting materials, and environmental enrichment can help reduce stress and improve overall well-being, which in turn can mitigate pain. Studies have shown that these modifications can positively impact post-surgical recovery and reduce pain-related behaviors.

Behavioral interventions, including the use of grimace scales, burrowing, and nest building, have been employed to assess and manage pain in rodents. These methods provide valuable insights into the pain status of animals and help in tailoring pain management protocols. The grimace scale, in particular, has been found to be a reliable indicator of post-surgical pain, although its implementation varies across studies (Aulehner et al., 2022).

3.3 Combining pharmacological and non-pharmacological methods

Combining pharmacological and non-pharmacological methods can enhance pain management in rodent models. Multimodal approaches that integrate the use of opioids, NSAIDs, and local anesthetics with environmental and behavioral interventions have been shown to provide comprehensive pain relief. However, the reporting of such multimodal treatments remains low, highlighting the need for improved training and implementation in laboratory settings (Figure 1) (King et al., 2023). Future research should focus on optimizing these combined approaches to ensure effective and humane pain management in rodent models (Huss et al., 2019).

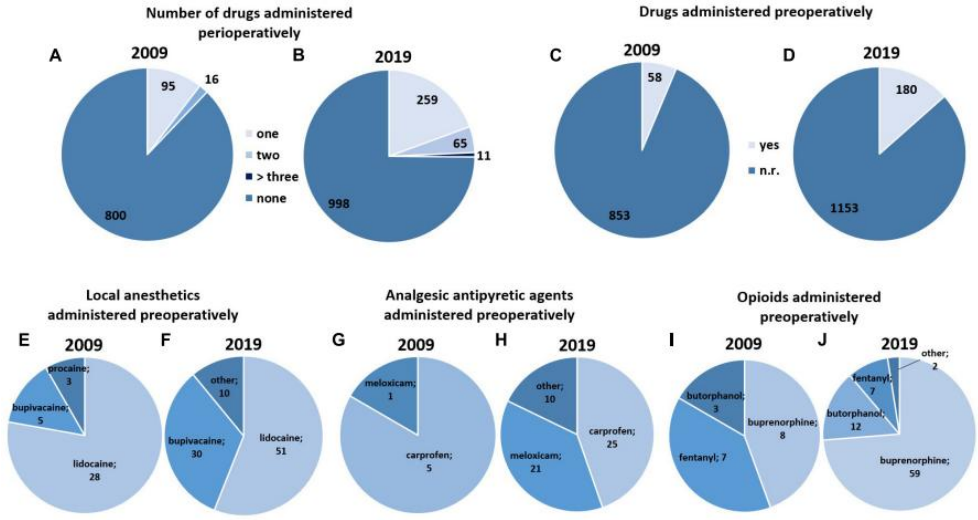

Figure 1 Analgesics and local anesthetics administered perioperatively and preoperatively (k = 2244 studies) (Adopted from King et al., 2023)

Image capton: (A,B) Number of drugs (analgesics and local anesthetics) administered perioperatively in 2009 (A) and 2019 (B). (C,D) Drugs (analgesics and local anesthetics) administered preoperatively in 2009 (C) and 2019 (D). (E,F) Local anesthetics administered preoperatively in 2009 (E) and 2019 (F). Other = drugs used in up to four studies. (G,H) Analgesic antipyretic agents administered preoperatively in 2009 (G) and 2019 (H). Other = drugs used in up to seven studies. (I,J) Opioids administered preoperatively in 2009 (I) and 2019 (J). Other = drugs used in up to two studies. “Preoperatively” was defined as all timepoints before skin incision (Adopted from King et al., 2023)

King et al. (2023) found that the administration of perioperative analgesics and local anesthetics increased from 2009 to 2019. The data shows a notable increase in the number of drugs administered perioperatively, with more patients receiving multiple drugs. In terms of local anesthetics, the administration of bupivacaine remained consistent, though there was an increase in the use of lidocaine by 2019. The utilization of analgesic antipyretic agents such as meloxicam saw a substantial rise, indicating a shift in preoperative medication protocols. Opioids, particularly buprenorphine, were administered more frequently in 2019 compared to 2009, reflecting an overall trend toward increased and more varied use of pain management drugs preoperatively. These findings underscore changes in clinical practice aimed at optimizing pain control, with a broader variety of medications being used in more recent years for perioperative and preoperative care.

4 Evaluating Efficacy of Pain Management Protocols

4.1 Outcome measures in rodent pain models

Outcome measures in rodent pain models are critical for assessing the efficacy of pain management protocols. Traditional methods often focus on stimulus-evoked responses such as the von Frey and Hargreaves tests, which measure mechanical and thermal sensitivity, respectively (Zhang et al., 2022). However, these methods have limitations in their clinical translatability as they do not fully capture the complexity of the human pain experience. Recent advancements have introduced non-stimulus-evoked methods, including grimace scales, burrowing, and gait analysis, which provide a more comprehensive assessment of pain by evaluating spontaneous behaviors and overall functionality. These methods are increasingly being adopted to enhance the predictive validity of preclinical pain models (Berge, 2011).

4.2 Behavioral indicators of pain relief

Behavioral indicators are essential for evaluating pain relief in rodent models. Traditional assessments have relied heavily on reflexive responses to sensory stimuli, which do not adequately reflect the multifaceted nature of pain. More recent approaches have focused on behaviors that are more indicative of the animal's overall well-being and pain state. For instance, the Complete Freund's Adjuvant (CFA) model has been used to study changes in exploratory behavior, stress coping, and naturalistic behaviors such as wheel running and burrowing (Figure 2) (Burek et al., 2021). Thigmotaxis, an innate predator avoidance behavior, has also been proposed as a measurable construct to assess the impact of pain and its alleviation through pharmacological interventions. These behavioral indicators provide a more holistic view of pain relief, capturing both the physical and emotional dimensions of pain (Cobos and Portillo-Salido, 2013).

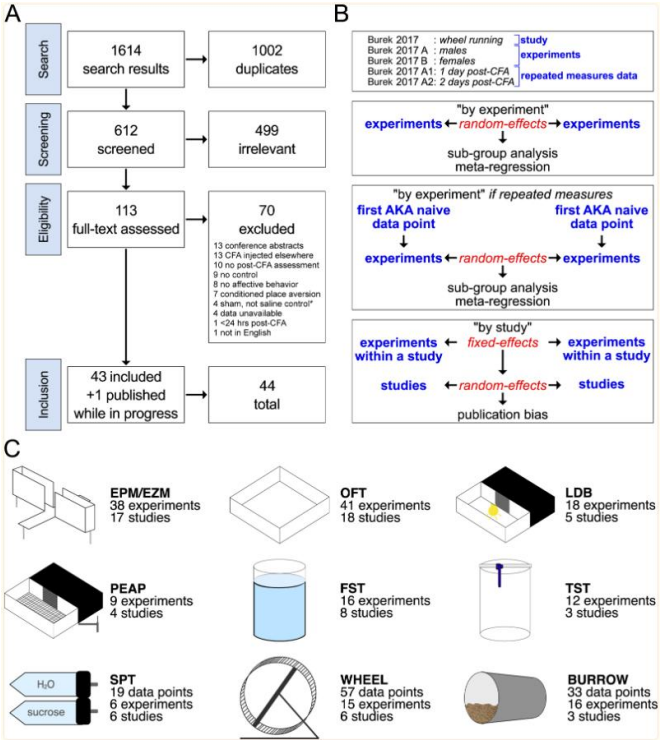

Figure 2 Search strategy, analysis strategy, and results (Adopted from Burek et al., 2021)

Image capton: A. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of search results, screening process, exclusion criteria, and final count of included studies. See methods for further information on “sham-not-saline” studies. B. Defined terminology and analysis strategy. C. Diagrams and metadata for the 9 behavioral tests included in this systematic review and meta-analysis: elevated plus/zero maze, open field test, light/dark box, place escape/avoidance paradigm, forced swim test, tail suspension test, sucrose preference test, wheel running, and burrowing. Main results include global summary effect estimates for all 9 tests and a subset of sub-group analysis and meta-regressions for the EPM/EZM, burrowing, and FST. Forest plots with individual experiments and studies, all sub-group analyses, and all meta-regressions per behavioral test are available in the supplemental file (Adopted from Burek et al., 2021).

Burek et al. (2021) found that the process of systematic review and meta-analysis in behavioral studies can be effectively streamlined using a structured approach to search strategies, screening, and eligibility criteria, as outlined in their PRISMA diagram. They highlight the importance of excluding studies based on specific criteria such as inappropriate controls and lack of critical data. Furthermore, their analysis strategy emphasizes the differentiation between "by experiment" and "by study" approaches, with fixed and random effects used to mitigate issues such as repeated measures and publication bias. The study's comprehensive inclusion of nine behavioral tests allowed for global summary effect estimates across multiple experimental paradigms, providing robust insights into behavioral outcomes. Additionally, subgroup analyses and meta-regressions were applied to specific tests like the elevated plus maze and forced swim test, enhancing the granularity of the findings. This methodological rigor ensures the reliability and relevance of meta-analytical conclusions in preclinical behavioral research.

4.3 Biochemical and physiological markers

Biochemical and physiological markers are crucial for understanding the underlying mechanisms of pain and the efficacy of pain management protocols. Traditional methods have focused on measuring sensory thresholds, but there is a growing recognition of the need for more comprehensive profiling (Rice et al., 2017). For example, sensory profiling in rodent models of neuropathic pain can provide valuable insights into the mechanisms of pain and help identify potential therapeutic targets. Additionally, automated systems using machine vision and machine learning have been developed to provide objective, high-throughput measurements of pain states and their reversal by analgesics. These advanced techniques offer a more detailed and accurate assessment of pain and its management (González-Cano et al., 2020).

4.4 Case study in place: application of a novel pain management protocol in a rodent model of neuropathic pain

A novel pain management protocol was applied in a rodent model of neuropathic pain to evaluate its efficacy (Cunha et al., 2020). The protocol incorporated both traditional and advanced outcome measures, including stimulus-evoked responses, behavioral indicators, and biochemical markers. The study utilized the CFA model to induce neuropathic pain and assessed the impact of the novel protocol on various pain-related behaviors and physiological markers. Automated systems were employed to provide objective measurements of pain states, capturing dynamic changes in behavior and physiology. The results demonstrated significant improvements in pain relief and overall well-being, highlighting the potential of the novel protocol for effective pain management in neuropathic conditions. This case study underscores the importance of using a multifaceted approach to evaluate pain management protocols, combining traditional methods with advanced technologies for a comprehensive assessment (Zhang et al., 2021).

5 Challenges and Limitations

5.1 Species-specific variability in response to pain management

One of the primary challenges in pain management protocols for rodent models is the significant variability in pain responses across different species and strains (Whittaker and Howarth, 2014). For instance, the Mouse Grimace Scale (MGS) has shown variability in baseline scores between sexes and strains of mice, indicating that males generally exhibit higher baseline scores than females, and different strains also show significant differences. This variability complicates the standardization of pain assessment and management protocols. Additionally, while nociceptive pathways and pain signaling mechanisms are highly conserved across mammalian species, the central processing of pain can differ, leading to varied responses to analgesics. This necessitates species-specific and even strain-specific pain management strategies, which can be labor-intensive and require extensive validation (Cunha et al., 2020).

5.2 Ethical considerations in pain research

Ethical considerations are paramount in pain research involving rodents. Ensuring that laboratory rodents receive adequate pain management is not only an ethical imperative but also a regulatory requirement aimed at maximizing animal welfare. However, the underutilization of analgesics in rodents, despite advances in pain

recognition and assessment, highlights a significant ethical challenge. Researchers often face a dilemma between the need to minimize animal suffering and the potential impact of analgesics on study outcomes. This is compounded by the lack of objective, science-driven data on pain assessment and the availability of appropriate pharmacological tools for pain mitigation. Moreover, the subtle signs of pain in prey species like rodents can make pain detection difficult, further complicating ethical pain management (Paterson and Turner, 2022).

5.3 Limitations of current pain assessment tools

Current pain assessment tools in rodent models have several limitations that hinder effective pain management. Traditional stimulus-evoked methods, such as the von Frey and Hargreaves tests, have been criticized for their limited clinical translatability and the stress-induced analgesia they may cause due to animal handling (Fried et al., 2020). Newer methods focusing on spontaneous behaviors, such as facial grimace scoring, burrowing, and nest-building, offer more promise but are often time-consuming and require further validation to determine their reliability and sensitivity across different experimental conditions and species. Additionally, the lack of validated pain assessment tools for chronic pain and the need for more automated and objective measurement techniques remain significant hurdles. Advanced videography and computational approaches are being developed to address these issues, but their adoption is still in the early stages. In summary, while significant progress has been made in understanding and managing pain in rodent models, challenges related to species-specific variability, ethical considerations, and the limitations of current pain assessment tools continue to pose significant obstacles. Addressing these challenges requires ongoing research, validation of new methods, and a commitment to ethical standards in animal research (Miller and Leach, 2015).

6 Future Directions

6.1 Emerging analgesic drugs

The development of new analgesic drugs is crucial for improving pain management in rodent models. Recent studies have highlighted the importance of validating animal pain models to enhance translational research and response to pharmacological treatments. For instance, the MI-RAT model combined with calibrated exercise has shown promise in demonstrating the efficacy of multimodal analgesia, including drugs like pregabalin and carprofen, which have shown significant anti-allodynic effects. Additionally, this study of pain management in rodents emphasizes the need for evidence-based data on effective regimens and the potential adverse effects of analgesics, suggesting that more research is needed to optimize dosing and minimize side effects. The exploration of new drug classes and their pharmacokinetic profiles will be essential in developing more effective pain management protocols for rodents.

6.2 Advances in technology for pain monitoring in rodents

Technological advancements are revolutionizing the way pain is monitored in rodent models. Automated systems using machine vision and machine learning have been developed to provide objective, sensitive, and high-throughput measurements of pain states in freely moving rodents. These systems can capture moment-by-moment changes in behavior, allowing for a more accurate assessment of pain and the efficacy of analgesics. Furthermore, the use of ethograms, facial grimace scoring, and other behavioral assessments in the home environment of rodents has shown promise in providing a more accurate and less stressful method of pain evaluation. These advancements not only improve the accuracy of pain assessment but also reduce the stress and potential analgesia induced by handling, leading to better overall animal welfare (Flecknell, 2018).

6.3 Personalized pain management approaches for rodent models

Personalized pain management approaches are becoming increasingly important in rodent models. The variability in pain responses among different species, strains, and even individual animals necessitates a more tailored approach to pain management. Studies have shown that factors such as species and strain can significantly influence the outcomes of pain-related behaviors and the efficacy of analgesics Personalized approaches that consider these individual differences, along with careful planning and veterinary guidance, can lead to more effective pain management strategies. Additionally, the use of larger animal models, such as companion canines, can provide valuable insights into the translational potential of analgesic agents and help bridge the gap between

rodent models and human clinical trials. By incorporating personalized approaches and leveraging insights from larger animal models, researchers can develop more effective and humane pain management protocols for rodent models. In conclusion, the future of pain management in rodent models lies in the development of new analgesic drugs, the adoption of advanced technologies for pain monitoring, and the implementation of personalized pain management approaches. These advancements will not only improve the efficacy of pain management protocols but also enhance the welfare of research animals, ultimately leading to more reliable and translatable research outcomes (Foley et al., 2019).

7 Conclusion

This study of pain management protocols in rodent models has revealed several critical insights. Firstly, the MI-RAT model demonstrated significant face and predictive validity, particularly when combined with calibrated exercise and multimodal analgesia, enhancing clinical translatability. Secondly, this study highlighted the importance of accurate pain assessment methods, noting that traditional algesiometry assays may oversimplify pain assessment and induce stress, whereas newer methods like ethograms and facial grimace scoring show promise but require further validation. Thirdly, the clinical management of pain in rodents remains underutilized due to various factors, including concerns about study outcomes and the labor-intensive nature of dosing regimens, despite the availability of effective pharmacologic and non-pharmacologic strategies. Additionally, this study underscored the need for back-translation of sensory profiling in rodent models to better align with clinical trial methodologies. Finally, the predictive validity of rodent models for chronic pain remains controversial, with significant variability in outcomes and a need for multiple models to reflect the heterogeneity of patient populations.

The findings from this study have several implications for both veterinary and biomedical research. For veterinary research, the validation of pain models like MI-RAT and the development of reliable pain assessment tools are crucial for improving animal welfare and ensuring ethical research practices. The use of multimodal analgesia and calibrated exercise protocols can enhance the efficacy of pain management in rodents, providing a more humane approach to animal research. In biomedical research, the insights gained from rodent models can inform the development of new analgesic drugs and pain management strategies. The emphasis on back-translation and the alignment of rodent sensory profiling with clinical trial methodologies can improve the predictive validity of preclinical studies, potentially leading to more successful translation of novel therapeutics to human clinical trials8. Additionally, this study suggests that incorporating larger animal models, such as companion canines, can provide stronger predictive information for human trials, particularly for chronic pain conditions. This approach can bridge the gap between rodent models and human clinical outcomes, enhancing the overall translational success of pain management research. In conclusion, the systematic review underscores the importance of validated pain models, accurate assessment methods, and the integration of multimodal analgesia in rodent research. These elements are essential for advancing both veterinary and biomedical research, ultimately leading to improved pain management protocols and better translational outcomes.

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Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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