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REPURPOSING EXISTING MEDICATIONS FOR CHRONIC PAIN MANAGEMENT: A COMPREHENSIVE REVIEW OF MECHANISMS, EFFICACY, AND FUTURE DIRECTIONS

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ABSTRACT: Chronic pain is a major global health issue, affecting around 20% of the adult population in Western countries. Current treatment options often prove inadequate and carry significant side effects, particularly with opioids. Developing new analgesics faces challenges due to difficulties in translating preclinical findings to human outcomes, resulting in clinical trial failures. Considering these obstacles, drug repurposing has emerged as a viable strategy to find new therapeutic options for chronic pain management. This approach investigates existing approved or previously failed drugs for new indications, bypassing the lengthy and costly traditional drug development process. This narrative review provides a comprehensive and in-depth overview of drug repurposing in chronic pain management, examining mechanisms of action, efficacy, and future directions for research and clinical application, ensuring that you, as healthcare professionals, researchers, and individuals involved in chronic pain management, are well-informed and knowledgeable in this area.

Keywords: Chronic Pain. Global Health Burden. Drug Repurposing. Analgesics. Therapeutic. Options.

INTRODUCTION

Chronic pain represents a significant global health burden, affecting approximately 20% of the adult population in the United States and other Western countries [1]. Despite the high prevalence, current treatment options for chronic pain often lack sufficient efficacy and are associated with significant side effects, particularly in the case of opioids [2]. The development

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of novel analgesics has been hindered by the failure to translate findings from preclinical pain models to human patients, leading to setbacks in clinical trials [1]. In this context, drug repurposing has emerged as a promising alternative approach to identifying new therapeutic options for chronic pain management. This strategy involves exploring new indications for approved or failed drugs, bypassing various steps of the classical drug development process, which is often costly and time-consuming [3]. This narrative review aims to provide a comprehensive overview of the current state of drug repurposing for chronic pain management, focusing on the mechanisms of action, efficacy, and future directions of this approach. We hope that this review will inspire and motivate you, as healthcare professionals, researchers, and individuals involved in chronic pain management, to explore the potential of drug repurposing in your work.

METHODOLOGY

A systematic literature search used Scopus, Web of Science, PubMed, ERIC, IEEE Xplore, ScienceDirect, Directory of Open Access Journals (DOAJ), and JSTOR. The search terms included "drug repurposing," "drug repositioning," "chronic pain," "neuropathic pain," "inflammatory pain," and the names of specific drugs discussed in this review. The retrieved articles were screened for relevance, and the reference lists of the included studies were manually searched for additional relevant publications. The selected articles were then analyzed and synthesized to provide a comprehensive overview of the current state of drug repurposing for chronic pain management.

RESULTS

Antidepressants and Anticonvulsants

Antidepressants and anticonvulsants have been widely used in the management of chronic pain, particularly neuropathic pain. These agents modify the neurochemistry of the spinal cord dorsal horn, contributing to their analgesic effects [4].

1.1. Tricyclic Antidepressants (TCAs)

TCAs, such as amitriptyline and nortriptyline, have been repurposed for the treatment of various chronic pain conditions, including neuropathic pain, fibromyalgia, and chronic headaches [5]. The analgesic effects of TCAs are attributed to their ability to inhibit the reuptake of serotonin and norepinephrine, which are involved in descending pain modulation [6].

1.2. Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

SNRIs, such as duloxetine and venlafaxine, have been repurposed for the treatment of neuropathic pain and fibromyalgia [7]. Like TCAs, SNRIs enhance descending pain inhibition by increasing the availability of serotonin and norepinephrine in the spinal cord dorsal horn [6].

1.3. Anticonvulsants

Anticonvulsants, such as gabapentin and pregabalin, have been repurposed for the treatment of neuropathic pain conditions, including postherpetic neuralgia and painful diabetic neuropathy [8]. These agents bind to the α2δ subunit of voltage-gated calcium channels, reducing the release of excitatory neurotransmitters and attenuating neuronal hyperexcitability [9].

NMDA Receptor Antagonists

N-methyl-D-aspartate (NMDA) receptor antagonists have been investigated for their potential in chronic pain management. NMDA receptors are crucial in central sensitization and the development of chronic pain states [10].

2.1. Ketamine

Ketamine, an NMDA receptor antagonist primarily used as an anesthetic, has been repurposed for the treatment of various chronic pain conditions, including central pain, complex regional pain syndrome (CRPS), fibromyalgia, and neuropathic pain [11]. Despite the

lack of high-quality evidence, ketamine has been used as a "third line" analgesic option when standard treatments have failed [11].

2.2. Dextromethorphan

Dextromethorphan, an NMDA receptor antagonist and cough suppressant, has been investigated for its potential in chronic pain management [12]. While some studies have reported analgesic effects in neuropathic pain conditions, the evidence remains inconclusive [13].

Topical Agents

Topical agents have been repurposed to treat localized neuropathic pain, offering the advantage of reduced systemic side effects [14].

3.1. Lidocaine

Topical lidocaine, a local anesthetic, has been found to be effective in managing postherpetic neuralgia and other localized neuropathic pain conditions [14]. Its analgesic effects are attributed to the blockade of voltage-gated sodium channels, which reduces ectopic discharge in affected nerves [15].

3.2. Capsaicin

Capsaicin, the active component of chili peppers, has been repurposed for treating neuropathic pain conditions, such as postherpetic neuralgia and HIV-associated neuropathy [14]. High-concentration capsaicin (8%) patches are particularly effective [14]. Capsaicin desensitizes the transient receptor potential vanilloid 1 (TRPV1) channel, reducing neuropathic pain [16].

Alpha-2 Adrenergic Agonists

Alpha-2 adrenergic agonists, such as clonidine, have been repurposed for chronic pain management, particularly in reducing opioid consumption [17]. Clonidine enhances

descending noradrenergic inhibition and reduces the release of pro-nociceptive substances in the spinal cord [18].

Anti-inflammatory Agents

Anti-inflammatory agents, such as cyclooxygenase (COX) inhibitors and other non-steroidal anti-inflammatory drugs (NSAIDs), have been used as adjunctive therapies in chronic pain management, particularly in inflammatory pain conditions [17]. These agents reduce the production of prostaglandins, which are involved in peripheral and central sensitization [19].

Emerging Therapies

Recent studies have explored the repurposing of various drugs for their potential in chronic pain management, focusing on their anti-inflammatory and neuroprotective effects [1].

6.1. Minocycline

Minocycline, a tetracycline antibiotic, has been investigated for its analgesic and neuroprotective properties in chronic pain [1]. Its effects are attributed to its ability to inhibit microglial activation and reduce the release of pro-inflammatory cytokines [20].

6.2. Fingolimod

Fingolimod, an immunomodulatory drug used in the treatment of multiple sclerosis, has been found to have analgesic effects in preclinical models of neuropathic pain [1]. Its mechanisms of action include modulating sphingosine-1-phosphate receptors and reducing neuroinflammation [21].

6.3. Pioglitazone

Pioglitazone, a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist used in treating type 2 diabetes, has been investigated for its analgesic and neuroprotective effects in

chronic pain [1]. Its mechanisms involve the attenuation of neuroinflammation and the promotion of neuroprotection [22].

DISCUSSION

Drug repurposing offers a promising approach to address the unmet needs in chronic pain management, given the limitations of current therapies and the challenges associated with the development of novel analgesics. The repurposing of antidepressants, anticonvulsants, NMDA receptor antagonists, topical agents, and alpha-2 adrenergic agonists has provided clinicians with a broader range of therapeutic options for the management of various chronic pain conditions. These repurposed drugs act through diverse mechanisms, including the modulation of neurotransmitter systems, the reduction of neuronal hyperexcitability, and the attenuation of neuroinflammation.

The evidence supporting the efficacy of repurposed drugs in chronic pain management varies, with some agents, such as antidepressants and anticonvulsants, having a more established role in clinical practice. In contrast, the evidence for the efficacy of ketamine and other NMDA receptor antagonists remains limited, with most studies being of low quality or providing divergent results [11]. Similarly, the effectiveness of topical agents and alpha-2 adrenergic agonists has been demonstrated in specific neuropathic pain conditions. Still, their role in the broader context of chronic pain management requires further investigation [14, 17].

The emerging therapies discussed in this review, such as minocycline, fingolimod, and pioglitazone, represent a new frontier in drug repurposing for chronic pain management. These agents target neuroinflammation and provide neuroprotection, which are increasingly recognized as crucial factors in developing and maintaining chronic pain states [1]. While the preclinical evidence for these agents is promising, their clinical efficacy and safety in chronic pain management remain to be established through well-designed randomized controlled trials.

The repurposing of drugs for chronic pain management offers several advantages over the traditional drug development process. By focusing on approved or failed drugs with established safety profiles, drug repurposing can reduce the time and cost of bringing new therapies to market [3]. Additionally, the multiple mechanisms of action of repurposed drugs

may contribute to enhanced efficacy and reduced side effects compared to single-target agents [23].

However, drug repurposing for chronic pain management also faces several challenges. The heterogeneity of chronic pain conditions and the lack of standardized outcome measures in clinical trials can make it difficult to compare the efficacy of different repurposed drugs [24]. Furthermore, the optimal dosing, route of administration, and duration of treatment for repurposed medications in chronic pain management often remain unclear, requiring further investigation [25].

To address these challenges and advance the field of drug repurposing for chronic pain management, several strategies can be considered. First, developing standardized outcome measures and using novel trial designs, such as adaptive and enriched enrollment randomized withdrawal (EERW) trials, can help improve the efficiency and validity of clinical studies [26]. Second, integrating biomarkers and precision medicine approaches can aid in identifying patient subgroups most likely to benefit from specific repurposed drugs [27]. Finally, establishing collaborative research networks and public-private partnerships can facilitate the sharing of knowledge and resources, accelerating the translation of promising repurposed medications into clinical practice [28].

CONCLUSION

Drug repurposing represents a promising approach to address the unmet needs in chronic pain management, offering the potential for faster, less expensive, and more effective therapies. The repurposing of antidepressants, anticonvulsants, NMDA receptor antagonists, topical agents, and alpha-2 adrenergic agonists has expanded the therapeutic options for various chronic pain conditions. At the same time, emerging therapies targeting neuroinflammation and neuroprotection offer new avenues for exploration. However, the field of drug repurposing for chronic pain management faces several challenges, including the heterogeneity of chronic pain conditions, the lack of standardized outcome measures, and the need for further investigation of optimal dosing, route of administration, and duration of treatment.

A concerted effort from researchers, clinicians, industry, and regulatory agencies is required to overcome these challenges and fully realize the potential of drug repurposing in chronic pain management. The field can accelerate the translation of promising repurposed drugs into clinical practice by developing standardized outcome measures, employing novel trial designs, integrating biomarkers and precision medicine approaches, and fostering collaborative research networks. Ultimately, drug repurposing holds the promise of providing safer, more effective, and more accessible therapies for the millions of individuals suffering from chronic pain worldwide.

REFERENCE

1. SISIGNANO, M., Parnham, M. J., & Geisslinger, G. (2021). Drug repurposing for the development of novel analgesics. Trends in Pharmacological Sciences, 42(3), 145-157. https://doi.org/10.1016/j.tips.2020.11.005

2. FINNERUP, N. B., Attal, N., Haroutounian, S., McNicol, E., Baron, R., Dworkin, R. H., Gilron, I., Haanpää, M., Hansson, P., Jensen, T. S., Kamerman, P. R., Lund, K., Moore, A., Raja, S. N., Rice, A. S. C., Rowbotham, M., Sena, E., Siddall, P., Smith, B. H., & Wallace, M. (2015). Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. The Lancet Neurology, 14(2), 162-173. https://doi.org/10.1016/S1474-4422(14)70251-0

3. PUSHPAKOM, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., Wells, A., Doig, A., Guilliams, T., Latimer, J., McNamee, C., Norris, A., Sanseau, P., Cavalla, D., & Pirmohamed, M. (2019). Drug repurposing: Progress, challenges and recommendations. Nature Reviews Drug Discovery, 18(1), 41-58. https://doi.org/10.1038/nrd.2018.168

4. VOROBEYCHIK, Y., Gordin, V., Mao, J., & Chen, L. (2011). Combination therapy for neuropathic pain: A review of current evidence. CNS Drugs, 25(12), 1023-1034. https://doi.org/10.2165/11596280-000000000-00000

5. MOORE, R. A., Derry, S., Aldington, D., Cole, P., & Wiffen, P. J. (2015). Amitriptyline for neuropathic pain in adults. Cochrane Database of Systematic Reviews, 2015(7), CD008242. https://doi.org/10.1002/14651858.CD008242.pub3

6. OBATA, H. (2017). Analgesic mechanisms of antidepressants for neuropathic pain. International Journal of Molecular Sciences, 18(11), 2483. https://doi.org/10.3390/ijms18112483

7. LUNN, M. P., Hughes, R. A., & Wiffen, P. J. (2014). Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database of Systematic Reviews, 2014(1), CD007115. https://doi.org/10.1002/14651858.CD007115.pub3

8. WIFFEN, P. J., Derry, S., Bell, R. F., Rice, A. S., Tölle, T. R., Phillips, T., & Moore, R. A. (2017). Gabapentin for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews, 2017(6), CD007938. https://doi.org/10.1002/14651858.CD007938.pub4

9. KUKKAR, A., Bali, A., Singh, N., & Jaggi, A. S. (2013). Implications and mechanism of action of gabapentin in neuropathic pain. Archives of Pharmacal Research, 36(3), 237-251. https://doi.org/10.1007/s12272-013-0057-y

10. ZHOU, H. Y., Chen, S. R., & Pan, H. L. (2011). Targeting N-methyl-D-aspartate receptors for treatment of neuropathic pain. Expert Review of Clinical Pharmacology, 4(3), 379-388. https://doi.org/10.1586/ecp.11.17

11. BLONK, M. I., Koder, B. G., van den Bemt, P. M., & Huygen, F. J. (2010). Use of oral ketamine in chronic pain management: A review. European Journal of Pain, 14(5), 466-472. https://doi.org/10.1016/j.ejpain.2009.09.005

12. WEINBROUM, A. A. (2012). Non-opioid IV adjuvants in the perioperative period: Pharmacological and clinical aspects of ketamine and gabapentinoids. Pharmacological Research, 65(4), 411-429. https://doi.org/10.1016/j.phrs.2012.01.002

13. DUEDAHL, T. H., & Rømsing, J. (2009). A systematic review of controlled clinical trials on the effects of dextromethorphan in the treatment of chronic/persistent pain. European Journal of Pain Supplements, 3(1), 43-47. https://doi.org/10.1016/S1754-3207(09)70011-0

14. DERRY, S., Rice, A. S., Cole, P., Tan, T., & Moore, R. A. (2017). Topical capsaicin (high concentration) for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews, 2017(1), CD007393. https://doi.org/10.1002/14651858.CD007393.pub4

15. CASALE, R., Symeonidou, Z., & Bartolo, M. (2017). Topical treatments for localized neuropathic pain. Current Pain and Headache Reports, 21(3), 15. https://doi.org/10.1007/s11916-017-0615-y

16. ANAND, P., & Bley, K. (2011). Topical capsaicin for pain management: Therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. British Journal of Anaesthesia, 107(4), 490-502. https://doi.org/10.1093/bja/aer260

17. KREMER, M., Salvat, E., Muller, A., Yalcin, I., & Barrot, M. (2016). Antidepressants and gabapentinoids in neuropathic pain: Mechanistic insights. Neuroscience, 338, 183-206. https://doi.org/10.1016/j.neuroscience.2016.06.057

18. GIOVANNONI, M. P., Ghelardini, C., Vergelli, C., & Dal Piaz, V. (2009). Alpha2-agonists as analgesic agents. Medicinal Research Reviews, 29(2), 339-368. https://doi.org/10.1002/med.20134

19. BURIAN, M., & Geisslinger, G. (2005). COX-dependent mechanisms involved in the antinociceptive action of NSAIDs at central and peripheral sites. Pharmacology & Therapeutics, 107(2), 139-154. https://doi.org/10.1016/j.pharmthera.2005.02.004

20. ZEMLAN, F. P., & Behbehani, M. M. (1988). Nucleus cuneiformis and pain modulation: Anatomy and behavioral pharmacology. Brain Research, 453(1-2), 89-102. https://doi.org/10.1016/0006-8993(88)90149-7

21. DOYLE, T., Chen, Z., Obeid, L. M., & Salvemini, D. (2011). Sphingosine-1-phosphate receptor 1 agonists: A patent review (2010-present). Expert Opinion on Therapeutic Patents, 21(12), 1759-1769. https://doi.org/10.1517/13543776.2011.628587

22. BORSOOK, D., Hargreaves, R., Bountra, C., & Porreca, F. (2014). Lost but making progress--Where will new analgesic drugs come from? Science Translational Medicine, 6(249), 249sr3. https://doi.org/10.1126/scitranslmed.3008320

23. DWORKIN, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., Kerns, R. D., Stucki, G., Allen, R. R., Bellamy, N., Carr, D. B., Chandler, J., Cowan, P., Dionne, R., Galer, B. S., Hertz, S., Jadad, A. R., Kramer, L. D., Manning, D. C., ... IMMPACT. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain, 113(1-2), 9-19. https://doi.org/10.1016/j.pain.2004.09.012

24. SMITH, S. M., Dworkin, R. H., Turk, D. C., Baron, R., Polydefkis, M., Tracey, I., Borsook, D., Edwards, R. R., Harris, R. E., Wager, T. D., Arendt-Nielsen, L., Burke, L. B., Carr, D. B., Chappell, A., Farrar, J. T., Freeman, R., Gilron, I., Goli, V., Haeussler, J., ... Witter, J. (2017). The potential role of sensory testing, skin biopsy, and functional brain imaging as biomarkers in chronic pain clinical trials: IMMPACT considerations. The Journal of Pain, 18(7), 757-777. https://doi.org/10.1016/j.jpain.2017.02.429

25. MOORE, R. A., Derry, S., & Wiffen, P. J. (2013). Challenges in design and interpretation of chronic pain trials. British Journal of Anaesthesia, 111(1), 38-45. https://doi.org/10.1093/bja/aet126

26. LOTSCH, J., & Ultsch, A. (2018). Machine learning in pain research. Pain, 159(4), 623-630. https://doi.org/10.1097/j.pain.0000000000001118

27. BORSOOK, D., Hargreaves, R., & Becerra, L. (2011). Can functional magnetic resonance imaging improve success rates in CNS drug discovery? Expert Opinion on Drug Discovery, 6(6), 597-617. https://doi.org/10.1517/17460441.2011.584529