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Conolidine: A Novel Plant Extract for Chronic Pain

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Abstract

Pain, the most common symptom reported among patients in the primary care setting, is complex to manage. Opioids are among the most potent analgesics agents for managing pain. Since the mid-1990s, the number of opioid prescriptions for the management of chronic non-cancer pain (CNCP) has increased by more than 400%, and this increased availability has significantly contributed to opioid diversion, overdose, tolerance, dependence, and addiction. Despite the questionable effectiveness of opioids in managing CNCP and their high rates of side effects, the absence of available alternative medications and their clinical limitations and slower onset of action has led to an overreliance on opioids. Conolidine is an indole alkaloid derived from the bark of the tropical flowering shrub *Tabernaemontana divaricate* used in traditional Chinese, Ayurvedic, and Thai medicine. Conolidine could represent the beginning of a new era of chronic pain management. It is now being investigated for its effects on the atypical chemokine receptor (ACK3). In a rat model, it was found that a competitor molecule binding to ACKR3 resulted in inhibition of ACKR3's inhibitory activity, causing an overall increase in opiate receptor activity. Although the identification of conolidine as a potential novel analgesic agent provides an additional avenue to address the opioid crisis and manage CNCP, further studies are necessary to understand its mechanism of action and utility and efficacy in managing CNCP.

Keywords: Conolidine, Chronic Pain, *Tabernaemontana divaricate*, Atypical Chemokine Receptor, Endogenous Opiates

1. Context

Pain, the most common symptom reported among patients in the primary care setting, is complex to manage and one of the most debilitating health problems in our modern world (1, 2). Acute pain is generally a predictable and anticipated short-term increase in background pain that occurs in response to noxious stimulation, including trauma, tissue damage, or a disease process, all of which induce sensory, inflammatory, hormonal, and immunologic alterations. Although acute pain typically resolves within a few days or weeks, the pain persists and becomes intractable for a significant portion of the patient population (3). Pathophysiological changes in the periphery and central nervous system lead to peripheral and central sensitization, thereby transitioning the poorly controlled acute pain into a chronic pain state or persistent pain condition (3). While noxious stimuli traditionally trigger the perception of pain, it can also be generated by lesions in the peripheral or central nervous systems. Chronic non-cancer pain (CNCP), which persists beyond the assumed normal tissue healing time of 3 months, is reported by more than 30% of Americans (4).

The treatment of chronic pain should reflect its biopsychosocial nature and may encompass both pharmacologic and non-pharmacologic management. Opioids have been regarded as among the most effective analgesic agents for managing pain (5). Since the mid-1990s, the number of opioid prescriptions for the management of CNCP has increased by more than 400%, and this increased availability has significantly contributed to opioid diversion, overdose, tolerance, dependence, and addiction (1, 6). Evidence additionally demonstrates that there has been a significant increase in the average cumulative dose of opioids prescribed per person over time (7). Notably, between 1999

and 2019, the number of overdose deaths involving prescription opioids has quadrupled (8). Although opioids were falsely perceived to be benign analgesic agents, opioid use increases the risk of an adverse event and serious adverse events (7, 9, 10).

Despite the questionable effectiveness of opioids in managing CNCP and their high rates of side effects, the absence of available alternative medications and their clinical limitations and slower onset of action has led to an overreliance on opioids. Chronic pain is challenging to treat. Advances in the understanding of the cellular and molecular mechanisms of pain and the characteristics of pain have led to the discovery of novel therapeutic avenues for the management of chronic pain. Conolidine, an indole alkaloid derived from the bark of the tropical flowering shrub *Tabernaemontana divaricate* that has been used in traditional Chinese, Ayurvedic, and Thai medicine, represents the beginning of a new era of chronic pain management (11). This article will discuss and summarize the current therapeutic modalities of chronic pain and the therapeutic properties of conolidine.

2. Evidence Acquisition

2.1. Chronic Pain Current Treatment

Historically, the dominant therapeutic modalities for managing chronic pain have been oral analgesics. However, various treatment approaches, pharmacologic and non-pharmacologic, are available to manage chronic pain.

2.1.1. Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) have powerful analgesic, anti-inflammatory, and antipyretic effects. NSAIDs work by inhibiting cyclooxygenase (COX) enzymes COX-1 and COX-2, which impairs the synthesis of prostanoids (12). While NSAIDs are generally safe and well-tolerated, their side-effect profiles limit their use, particularly when used long-term or when high doses are required to control pain (13). The side effects include gastrointestinal ulceration and bleeding, renal insufficiency, coronary heart disease, and thrombotic cardiovascular events (14, 15).

2.1.2. Opioids

Opioids are commonly prescribed for chronic pain management and produce their pharmacological actions, including analgesia, by activating opioid receptors on nerve cells (16). Although opioids are effective for moderate to severe acute pain, evidence of their long-term efficacy is limited and controversial (17). The interpretation of studies assessing the utilization of opioids for managing chronic pain is limited due to high patient drop-out rates, largely secondary to adverse events or insufficient pain relief (18). However, the use of opioids rarely provides long-term pain relief for patients with CNCP as their side-effect profile limits significant dosage adjustments (19). Common side-effects and risks associated with the use of opioids include sedation, dizziness, respiratory depression, constipation, nausea, vomiting, tolerance, physical dependence, hyperalgesia, and addiction, leading to opioid use disorder (OUD) (20, 21). Compared to full agonists such as morphine, oxycodone, and fentanyl, buprenorphine, an opioid partial agonist used in the treatment of both pain and OUD, has a lower likelihood of producing serious side effects (22). However, it remains underutilized due to misconceptions regarding its use and structural obstacles in the healthcare system.

2.1.3. Topical and Transdermal Analgesics

Topical and transdermal analgesic agents, including NSAIDs, opioids, rubefacients, capsaicin, clonidine, and lidocaine, are attractive treatment options and alternatives to oral analgesic agents for chronic pain (23). While topical drugs exert analgesic effects by penetrating the skin via passive diffusion, transdermal delivery is achieved through percutaneous absorption and relies on systemic distribution (24). Topical and transdermal analgesic agents offer the advantage of reducing systemic adverse effects. However, they are associated with application-site reactions, including irritation, burning, erythema, and discoloration (25). Although a recent Cochrane review found that topical salicylate, low-concentration capsaicin, clonidine, and lidocaine are not well supported by evidence, there may be beneficial outcomes for certain patients (24).

2.1.4. Anticonvulsants

Gabapentinoids (gabapentin, pregabalin, and mirogabalin), originally developed as anticonvulsant drugs, are commonly utilized to manage various chronic pain conditions (26-29). They exert their analgesic effects by binding to the α-2-δ subunit of voltage-dependent calcium channels. Gabapentinoids may cause sedation, respiratory depression, and altered cognition, and they possess the potential for abuse (30-35).

2.1.5. Antidepressants

Tricyclic antidepressants (TCAs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are classes of antidepressants that have been shown to exhibit analgesic properties and be effective in the management of a variety of neuropathic conditions (36, 37). TCAs and SNRIs provide analgesia by increasing the activity of the serotonergic and noradrenergic descending pathways in the brainstem and

midbrain (36, 38). Notably, the analgesic effects of antidepressants occur at lower doses than those required for the treatment of depression and are effective even in patients who are not clinically depressed (39). However, treatment with antidepressants may be limited due to their varying side-effect profiles, including dry mouth, dizziness, sedation, constipation, urinary retention, orthostatic hypotension, hypertension, and cardiac conduction abnormalities (38).

2.1.6. Interventional Pain Management

Interventional procedures vary by complexity and invasiveness, including trigger point injections, epidural steroid injections, sympathetic nerve blocks, radiofrequency ablation, cryoneuroablation, intrathecal drug delivery systems, and spinal cord stimulators, and deep brain stimulation (40-46). Although interventional therapies have associated risks, such as infection, dural puncture, spinal cord trauma, or nerve injury, the significant improvement in quality of life for certain patients makes them attractive treatment options, particularly in those who do not respond well to topical or oral analgesic agents (47-53).

2.1.7. Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) is a surface-applied unit that delivers low voltage electrical current through the skin to produce analgesia. Although TENS may provide effective analgesia for some patients, insufficient evidence supports its efficacy in chronic pain management (54).

2.1.8. Psychosocial Treatments

Psychosocial treatment modalities, which include cognitive behavioral therapy, mind-body therapy, and physical and occupational therapy, can improve the overall pain experience by addressing the psychological and social factors that influence and account for the variability in the experience of pain (55, 56).

2.2. Conolidine

Conolidine has unique qualities that can be beneficial for the management of chronic pain. Conolidine is found in the bark of the flowering shrub *T. divaricata*, otherwise known as the pinwheel flower or crepe jasmine, and is used in traditional Chinese, Ayurvedic, and Thai medicine to treat pain and fever (57). The compound makes up .00014% of *T. divaricata* bark. *Tabernaemontana divaricatea* contains several alkaloid compounds with a carbon-based framework resembling opioids (57). It is plausible that conolidine induced analgesia may lack complications associated with classic opioid medications (58). It is now being investigated for its effects on the atypical chemokine receptor (ACK3), an opioid scavenger of the dynorphin, enkephalin, and nociceptin families (59, 60). The ACK3 receptor has been found to regulate the availability of these opiates to classical opiate receptors. It is found in high concentrations in several important opiate-related centers of the brain (59). It was demonstrated that this novel receptor does not trigger the G protein cascade signaling pathway, and peptides specific to this receptor block the downregulatory effect it has on endogenous opiate levels, resulting in increased availability of opiate peptides for other classical opioid receptors (58). Modulation of this receptor has been postulated as an alternative opiate system target, and evaluations by Szpakowska et al. found it to be highly responsive to conolidine (58). Conolidine is a potent non-opioid analgesic and has been found to lack the typical complications associated with opiate analgesics like nausea, vomiting, respiratory depression, constipation, tolerance, and physical dependence (60).

2.3. Mechanism of Action

Elucidating the precise pharmacological mechanism of action (MOA) of naturally occurring compounds can be challenging. Although Tarselli et al. (60) developed the first de novo synthetic pathway to conolidine and showcased that this naturally occurring compound effectively suppresses responses to both chemically induced and inflammation-derived pain, the pharmacologic target responsible for its antinociceptive action remained elusive. Given the difficulties associated with standard pharmacological and physiological approaches, Mendis et al. utilized cultured neuronal networks grown on multi-electrode array (MEA) technology coupled with pattern matching response profiles to provide a potential MOA of conolidine (61). A comparison of drug effects in the MEA cultures of central nervous system active compounds identified that the response profile of conolidine was most similar to that of ω-conotoxin CVIE, a $Ca_v2.2$ calcium channel blocker (61). More recently, conolidine has been identified to target the highly expressed atypical chemokine receptor ACKR3, which functions as a scavenger that prevents endogenous opioid peptides from binding to the classical opioid receptors (MOR, DOR, KOR, and NOP) (58, 59). As a modulator of ACKR3, conolidine increases the availability of endogenous opioid peptides, thereby inducing analgesia. Notably, ACKR3 is not modulated by prescription opioids and does not trigger classical G protein signaling but rather mainly relies on β-arrestin recruitment (59). Although recent studies have paved a pathway for conolidine as a potential novel analgesic agent in managing chronic

pain, further studies are necessary to elucidate its precise MOA or numerous biologic targets.

Conolidine and cannabidiol are natural compounds with anti-nociceptive properties that may advance the future of chronic pain management (61). The shared mechanisms between the two may explain shared action regarding analgesia. The two compounds were compared using numerous firing parameters via multi-electrode arrays (61). The values were extracted from neuronal networks cultured and subjected to specific pattern recognition to similar compounds (61). Currently, the identification of novel compounds requires multiple functional screening assays incorporating isolated biological agents (61). These comparisons are made in a static environment, whereas ion gated channels operate in a specialized and interactive domain (61). Cultured networks create similar and realistic substrates to test CNS compounds (61). The drawback of the cultured network method is extracting and analyzing signature patterns for a given compound used for similar indexes (61). Multi-electrode arrays rely on single parameters for identifying differences in drug actions (61). During multi electrode array, conolidine and cannabidiol blocked Ca 2.2 channels (61).

Ca 2.2 channel blockade is important because Ca channels play key roles in pain perception by modulating calcium entry through neuron depolarization (61). Compounds that interact with the presynaptic Ca pathway are potential pain modulators due to Ca-dependent vesicle fusion effects (61). Secondarily, w-Conotoxin through Ca inhibits nociceptive signaling and reverses allodynia in animal models (61). Based on past research, Ca 2.2 channels are upregulated in sciatic nerve models of neuropathic pain (61). Knockout of the Ca 2.2 gene has been shown to reduce inflammation and neuropathic pain (61). Multidimensional scaling analysis has demonstrated the conolidine effect towards T-type calcium channel Ni whom Cannabidiol is known to inhibit (61). The inhibition of T type calcium channel could be caused by Ca 2.2 and Ca 3 inhibition (61). The model suggests Ca 2.2 and Ca 3 channels play an important role in conolidine's mechanism of action (61).

2.4. Clinical Studies Summary

Research on conolidine is limited, but the few studies currently available show that the drug holds promise as a possible opiate-like therapeutic for chronic pain. Conolidine was first synthesized in 2011 as part of a study by Tarselli et al. (60) The first de novo pathway to synthetic production found that their synthesized form served as effective analgesics against chronic, persistent pain in an in-vivo model (60). A biphasic pain model was utilized, in which formalin solution is injected into a rodent's paw. This results in a primary pain response immediately following injection and a secondary pain response 20 - 40 minutes after injection (62). The second pain phase is due to an inflammatory response, while the primary response is acute injury to the nerve fibers. Conolidine injection was found to suppress both the phase 1 and 2 pain response (60). This suggests conolidine effectively suppresses both chemically or inflammatory pain of both an acute and persistent nature. Further evaluation by Tarselli et al. found conolidine to have no affinity for the mu-opioid receptor, suggesting a different mode of action from traditional opiate analgesics. Furthermore, this study revealed that the drug does not alter locomotor activity in mice subjects, suggesting a lack of side effects like sedation or addiction found in other dopamine-promoting substances (60).

In another study completed by Arita et al., a related derivative of conolidine, known as DS39201083, was discovered (63). It was found to be even more potent than conolidine while also showing no mu-opioid receptor activity. Several other groups have also been successful in synthesizing derivatives of conolidine (64, 65). This study aimed to produce conolidine derivatives with an even greater analgesic effect and oral bioavailability. Using various synthesis techniques, derivatives were produced and tested for effect, ultimately resulting in the selection of compound 17a, which exhibited a more potent analgesic efficacy of 92% (63). This compound was also tested for mu-opioid receptor activity, and like conolidine, was found to have no activity at the site. Utilizing the same paw injection test, several alternatives with greater efficacy were found that inhibited the initial pain response, indicating opiate-like activity. Given the different mechanisms of these conolidine derivatives, it was also suspected that they would provide this analgesic effect without mimicking opiate side effects (63). The same group synthesized additional conolidine derivatives, finding an additional compound known as 15a that had similar properties and did not bind the mu-opioid receptor (66).

Most recently, it has been identified that conolidine and the above derivatives act on the atypical chemokine receptor 3 (ACKR3. Expressed in similar areas as classical opioid receptors, it binds to a wide array of endogenous opioids. Unlike most opioid receptors, this receptor acts as a scavenger and does not activate a second messenger system (59). As discussed by Meyrath et al., this also indicated a possible link between these receptors and the endogenous opiate system (59). This study ultimately determined that the ACKR3 receptor did not produce any G protein signal response by measuring and finding no mini G protein interactions, unlike classical opiate receptors, which recruit these proteins for signaling. Importantly, these receptors were found to have been activated by a wide range

of endogenous opioids at a concentration similar to that observed for activation and signaling of classical opiate receptors. In turn, these receptors were found to have scavenging activity, binding to and decreasing endogenous levels of opiates available for binding to opiate receptors (59). This scavenging activity was found to offer promise as a negative regulator of opiate function and as an alternative manner of control to the classical opiate signaling pathway.

Szpakowska et al. also studied conolidone and its action on the ACKR3 receptor, which helps to explain its previously unknown mechanism of action in both acute and chronic pain control (58). It was found that receptor levels of ACKR3 were as high or even higher as those of the endogenous opiate system and were correlated to similar areas of the CNS. This receptor was also not modulated by classic opiate agonists, including morphine, fentanyl, buprenorphine, or antagonists like naloxone. In a rat model, it was found that a competitor molecule binding to ACKR3 resulted in inhibition of ACKR3's inhibitory activity, causing an overall increase in opiate receptor activity. While the opiate receptor relies on G protein coupling for signal transduction, this receptor was found to utilize arrestin activation for internalization of the receptor. Otherwise, the receptor promoted no other signaling cascades (59) Modifications of conolidine have resulted in variable improvement in binding efficacy. This binding ultimately increased endogenous opioid peptide concentrations, increasing binding to opiate receptors and the associated pain relief.

While it is unknown whether other unknown interactions are occurring at the receptor that contribute to its effects, the receptor plays a role as a negative down regulator of endogenous opiate levels via scavenging activity. This drug-receptor interaction offers an alternative to manipulation of the classical opiate pathway. It may provide many of the same benefits of pain relief without the pitfalls of opiate use. Future facets of study could revolve around molecular analogs to conolidine, including percine, apparicine, and stemmadenine (58).

3. Conclusions

CNCP is a multifactorial process. Biological, psychological, and social factors influence and account for the variability in the experience of pain. Despite advances in research and the discovery of novel agents to manage CNCP, it remains a significant and life-altering problem. An array of pain management techniques, pharmacologic and nonpharmacologic, are available, each with notable limitations and therapeutic profiles that minimize their use in certain patients. However, opioids, despite the lack of evidence supporting their efficacy in managing CNCP and substantial liabilities associated with their use, have become one of the most utilized therapeutic modalities. In light of the current opioid epidemic, there is an urgent need to identify novel agents and mechanisms with improved safety profiles to treat CNCP. Researchers have recently identified and succeeded in synthesizing conolidine, a natural compound that shows promise as a potent analgesic agent with a more favorable safety profile. Although the exact mechanism of action remains elusive, it is currently postulated that conolidine may have numerous biologic targets. Presently, conolidine has been shown to inhibit $Ca_v2.2$ calcium channels and increase the availability of endogenous opioid peptides by binding to a recently identified opioid scavenger ACKR3. Although the identification of conolidine as a potential novel analgesic agent provides an additional avenue to address the opioid crisis and manage CNCP, further studies are necessary to understand its mechanism of action and utility and efficacy in managing CNCP.

Footnotes

Authors' Contribution: Study concept and design: ANE, ASP, MWB, EMC, AMK, ADK; Analysis and interpretation of data: MWB, JL, CW; Drafting of the manuscript: ANE, ASP, MWB, JL, CW, KS, ADK; Critical revision of the manuscript for important intellectual content: KS, EMC, AMK, ADK; Statistical analysis: ANE, ASP, MWB, JL, CW.

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