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Amitriptyline Therapy in Chronic Pain

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Abstract

Rodent evidence has confirmed the analgesic effect of tricyclic antidepressants in the treatment of chronic pain, which amitriptyline is rigorously verified. The analgesic effect of amitriptyline, whose mechanisms are complex and unclear, is different from its antidepressant effect. This article reviewed the mechanisms behind amitriptyline's analgesic properties to further understanding of this drug. Additionally, this article reviewed the clinical evidence of the effectiveness of amitriptyline therapy in treatment of chronic pain to offer guidance for future clinical practice.

Keywords

Amitriptyline, Chronic pain, Neuropathic pain, Primary headaches

Introduction

Chronic pain is a condition described as a long-standing pain that persists over the normal time of healing or occurs along with a chronic health condition [1]. A WHO collaborative study of pain in primary care revealed that chronic pain was present in about 5-33% of individuals in developing countries and 18-20% of individuals in developed countries [2]. According to a survey by the International Association for the Study of Pain (IASP), the most frequent types of chronic pain included neuropathic pain, musculo-skeletal pain, cancer pain, myofascial pain, pain of surgery, and headache [1]. Chronic pain is one of the most common reasons for individuals seeking healthcare, because it also interferes with daily activities, induces emotional disorders, and reduces quality of life [1].

Amitriptyline (AMI), as a member of the tricyclic antidepressants (TCAs) class of medicines, has been widely used as first-line treatment for chronic pain for many years [3]. Evidence reveals that tricyclic antidepressants also play an important role in treatment of non-mental illnesses, in which AMI has been most proven to be effective [4]. Growing evidence indicates that antidepressants are being frequently prescribed for conditions or health problems outside the field of psychiatry [5], which include pain, dependence, other neurological conditions, gastroenterological conditions, and urological conditions [6]. AMI may be beneficial in the following chronic pain conditions: migraine and tension-type headaches, painful polyneuropathy, painful diabetic neuropathy (PDN), HIV-related neuropathies, trigeminal neuralgia, post-herpetic neuralgia (PHN), phantom limb pain, non-specific low back pain, fibromyalgia, and many others [7]. There is a consensus that the analgesic effect of AMI is independent of its antidepressant effect [8,9]. However, the analgesic mechanisms are complex and unclear. The aim of this review was to highlight the advancements in the understanding of the mechanisms of AMI for chronic pain therapy and to summarize current evidence for its clinical application.

Mechanism of AMI's Analgesic Effects

Amitriptyline is a multi-modal analgesic drug with complex and unclear analgesic mechanisms. It is commonly known that AMI has an analgesic effect independent of its antidepressant effect [8]. From the perspective of clinical studies, the reasons may be: (1) most studies have found little relation between depressive symptoms and pain improvement, (2) AMI relieves pain in patients without depression, (3) the doses and treatment durations used for therapy of pain are often insufficient to treat depression. Preclinical studies have also supplied some evidence. For instance, one study found that although all studied antidepressants (amitriptyline, fluoxetine, and bupropion) could produce anti-allodynic effects in chronic constriction injury (CCI) afflicted mice, only AMI could improve the increased depression-like behavior induced by CCI [10]. These results suggest the dissociation between the anti-allogynic and antidepressant effects of AMI and confirm its dual effect in the treatment of neuropathic pain. The mechanisms that underlie the anti-nociceptive effects of AMI remain speculative.

Inhibition of monoaminergic reuptake

As a member of tricyclic antidepressants, AMI is known to inhibit the presynaptic reuptake of serotonin (5-HT) and norepinephrine (NE) and thus increase the concentrations of both neurotransmitters at the synaptic cleft. 5-HT and NE, important neurotransmitters of pain modulation system, can enhance the descending inhibitory system for pain [11]. By increasing the concentration of 5-HT and NE in synaptic terminal, AMI shows a supraspinal analgesic effect [12]. TCAs have a better clinical efficacy than selective serotonin reuptake inhibitors (SSRI) for chronic pain management, indicating that NE might play a more important part in AMI's analgesic properties [4].

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Interaction with ion channels

Recent years, many studies have found that AMI may affect the activity of ion channels, mainly sodium ion channels [13]. Located in small diameter nociceptive nerve fibers of peripheral nervous system, voltage-gated sodium channels (VGSCs) participate in the generation and conduction of nociceptive signals, which can be targeted in pain regulation. When these fibers are damaged, the VGSCs can lead to abnormal firing and pain, which may be part of the pathogenesis of neuropathic pain [14]. Using a whole-cell patch clamp technique, Bielefeldt et al. [15] discovered that AMI blocked the VGSCs in rat gastric neurons in an use-dependent manner. This may be the peripheral mechanism contributing to the analgesic effect of AMI. Our previous study also showed that AMI inhibited the tetrodotoxin-resistant (TTX-r) sodium channel Nav1.8/1.9 currents in a concentration-dependent manner in rat trigeminal ganglion neurons [16,17]. In addition, both TTX-s (tetrodotoxin-sensitive) and TTX-r sodium currents were blocked by AMI in a dose- and holding potential-dependent manner in rat dorsal root ganglion neurons [18]. A reduction of VGSC mRNA expression was discovered by using AMI in cultured rat cortical neurons [19]. There was a speculation that AMI may reduce cortical spreading depression (CSD) by inhibiting sodium channels, which may be another basis for migraine prophylaxis.

AMI may also have interactions with potassium channels. A pharmacological study found that the potassium channel blocker TEA reduced the anti-nociceptive effect of AMI, while the potassium channel agonist minoxidil promoted the anti-nociceptive effect of AMI [20]. They deduced that potassium channels mediated the central antinociception of AMI. However, blocking potassium channels can enhance central activity and may counteract the effect of AMI. Therefore, this process may have multiple interpretations which need further evaluation.

Change of pain-modulation-related receptors

Accumulated evidence has demonstrated that AMI likely affects multiple receptors associated with pain modulation. For example, AMI has been found to interact with opioids receptors, to inhibit the cellular uptake of adenosine, and to block N-methyl-D-aspartate (NMDA) receptors, etc. [4,13].

Several studies have confirmed the involvement of 5-HT and NE in the formation of morphine tolerance [21,22] and AMI, as a monoamine reuptake inhibitor, in the enhancement of morphine's analgesic effect. To examine the effects of serotonin/norepinephrine reuptake inhibitors on morphine analgesia tolerance in rats, an animal research found that co-administration of morphine with AMI increased the analgesic effects of morphine and attenuated the morphine analgesic tolerance [23]. In another study, the opioid receptor antagonist naloxone was found to shift the anti-nociception dose-response curve of AMI to the right, suggesting that AMI may increase the release of endogenous opioid peptides to ease pain [24].

Interactions with adenosine may also be an important part of AMI's analgesic mechanisms, as rodent studies have found that caffeine, an antagonist of adenosine receptor, could inhibit anti-nociception by AMI in several pain models [25-27]. Antinociception by systemic AMI was blocked by intrathecal administration of a selective adenosine A1 receptor antagonist in formalin mice model [28]. Moreover, chronic oral caffeine also decreased analgesia of AMI. Therefore, the conclusion that adenosine A1 receptor contributed to antinociception by systemic amitriptyline in both spinal and peripheral compartments were deduced.

NMDA receptor, one of the important member of excitatory aminoacid (EAA) receptors, plays an important role in the genesis of neuropathic pain. Multiple studies have examined the clinical efficacy of NMDA receptor antagonists such as ketamine and dextromethorphan as an adjunct to routine postoperative pain management [29]. Sawynok's research found that combination of an inactive dose of dextromethorphan with amitriptyline in formalin model, and vice versa, resulted in an increase of analgesia so that previously inactive doses now caused significant analgesia, which indicate the interaction between AMI and NMDA receptors [30]. Amitriptyline may also inhibit the glycine (Gly) transporter and thus improve the content of Gly, which can resist the excito-toxic effects of EAAs and has a potential neuro-protective effect [31,32].

Immunological mechanism

Several recent studies have considered a neuro-immunological influence on the pain-relieving mechanisms of antidepressants [33,34]. Research found TCAs may influence the function of glial cells [35,36]. Intrathecal co-administration of AMI inhibited the down-regulation of the glial glutamate transporters in chronically morphine-infused rats' spinal cord dorsal horn [37]. Activation of glial cells and increased cytokine (TNF-α, IL-1β, and IL-6) expression in the rat spinal induced by chronic morphine infusion was also prevented by AMI co-infusion. AMI may attenuate morphine tolerance and preserve its anti-nociceptive effect through these neuro-immunological impacts. The further research indicated the activation of the NF-κB pathway in this process [38]. Some pre-clinical studies also suggested the involvement of microglial cells in the efficacy of antidepressants [39,40]. Another study showed that chronic AMI administration prevented the increased expression of GFAP, IL-10, and CCL5 in the prefrontal cortex of OB-SNL (olfactory bulbectomised- spinal nerve ligation) rats [41]. Inhibition of peripheral inflammation may partly contribute to the analgesic effect of AMI, as presence of inflammation is a common underlying mechanism of pain [7]. AMI were discovered to inhibit 5-HT secretion, uptake, and reuptake in isolated rat peritoneal mast cells, indicating its periphery anti-inflammation function [42].

Improvement of comorbidities

Chronic pain patients are often susceptible to psychological disorders, which in turn will increase pain [1]. As an antidepressant, AMI can help ease the anxiety and depression conditions of pain sufferers and thus help relieve pain. Additionally, AMI has sedative properties, which may help regulate sleep [43]. Improvement of comorbidities can greatly reduce the burden brought on by pain and significantly improve quality of life in pain sufferers.

Clinical Application of AMI for Chronic Pain

Neuropathic pain

Neuropathic pain was defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" by the IASP [44]. The most common neuropathic pain conditions consist of PDN, PHN, and post-surgical neuropathic pain [45]. The major methods of neuropathic pain management include: antidepressants, anticonvulsants, opioids, and adjuvant analgesics [46,47]. Clinical studies have shown that TCAs tend to work better than anticonvulsants and opioids [48]. TCAs remain one of the first-line therapies for PDN and PHN [49]. AMI has widely been used to treat chronic neuropathic pain exactly as it was recommended in many guidelines [50,51].

Painful diabetic neuropathy (PDN): About 10-20% of diabetes patients suffer from painful diabetic neuropathy, which also impairs sleep, mood, and even quality of life [52]. The first and foremost treatment for all PDN patients is controlling blood glucose concentrations. Anticonvulsants and antidepressants are the most commonly used medications for pain management in diabetic neuropathy [53].

First-line analgesic treatments for PDN include antidepressants such as AMI, duloxetine, and calcium channel a2-δ ligands such as pregabalin and gabapentin [54]. Tricyclic antidepressants, amitriptyline and desipramine in particular, have been well studied and shown to be effective for treating PDN [55]. Although not recommended by the US Food and Drug Administration (FDA), AMI (25 to 150mg at bedtime) is an option for PDN sufferers [56].

Available evidence for treating PDN is limited to small studies and few head-to-head trials. In a randomized, placebo-controlled clinical trial, the researchers reported that AMI not only extenuated the pain in chronic PDN patients but also improved secondary parameters [57]. AMI improved sleep by reducing wake after sleep onset at higher dose (75mg), and also improved daytime performance with reduced recognition time and total reaction time. However, another clinical trial reported a higher incidence of adverse events such as dry mouth in AMI than duloxetine [58]. As a meta-analysis of the efficacy and safety of six antidepressants for management of PDN reported, AMI was the least safety agent for this indication [59]. Preclinical studies also proved the therapeutical effect of AMI on PDN [60,61]. Anti-allodynic effect of both peripheral and systemic AMI was found in streptozotocin (STZ)-induced diabetic rat model of neuropathic pain [60], which also suggested that topical application of TCAs might be useful in treating PDN.

Post-herpetic neuralgia (PHN): PHN is a chronic, disturbing pain condition that can persist long after resolution of visible cutaneous manifestations caused by the herpes zoster (HZ) virus. More than 5% of elderly patients have PHN at 1 year after acute HZ, of which management is challenging and often unsatisfactory [62]. Prevention and therapy for acute HZ are necessary to reduce the risk of PHN and other complications, while pain management is equally important [63,64]. PHN can be treated with either topical or systemic agents, and medications clinically used consist of amitriptyline, capsaicin, gabapentin, morphine, nortriptyline, pregabalin and others [65].

Amitriptyline, nortriptyline, desipramine and imipramine are TCAs that have been shown to be effective for the symptomatic relief of PHN [66]. An observational descriptive study including UK general population found that AMI (10-50mg/day) was one of the first-line options for pain management of PHN [67]. AMI is recommended for PHN patients with more severe pain, and for patients at high risk of developing PHN, early initiation of amitriptyline after the onset of herpes zoster is suggested [68,69]. Some evidence has supported that AMI can be effective in pre-emptive analgesia in PHN [70]. In addition, topical 2% amitriptyline/0.5% ketamine gel was reported effective for treatment of PHN in a case report [71].

Primary headaches

Migraine and tension-type headaches are the two most common primary headaches and bring a great burden to healthcare. The use of antidepressants for headache prophylaxis has been recommended, of which AMI is the only one yielding consistent evidence for treatment of migraine and chronic tension-type headache (CTTH) [8]. In a meta-analysis of randomized placebo-controlled trials on antidepressants as prophylactic treatment for chronic headaches, antidepressants have been reported as equally effective in chronic migraine and CTTH [72]. And only AMI has been studied in enough patients to show significant benefits.

Migraine: Migraine is a common primary headache in every part of the world, with a prevalence of 11% worldwide [73] and 9.3% in China [74]. It is a common disabling primary headache disorder and thus good management is necessary. Drug preventives of migraine is recommended if more than three attacks occur per month, acute drug treatment is insufficient, or very severe attacks with aura are the main problem [75].

The first choice for preventive therapy of migraine includes β-adrenoceptor blockers, flunarizine, topiramate, and valproic acid. Rodent evidence has verified the efficacy of AMI as a preventive for migraine, and evidence-based guidelines classified it into second-line therapy options [76,77]. In a cost-effectiveness analysis of interventions for migraine, AMI was found to be more cost-effective than propranolol or topiramate, because it was more effective than proanolol and far cheaper than topiramate [78]. AMI is also effective in managing migraine in children and adolescents [79,80]. Furthermore, prophlaxis with AMI can reduce the Migraine Disability Assessment Score (MIDAS) thus improve the quality of life in migranieurs [81]. According to a systemic review of clinical trials, the starting dose of AMI therapy for migraine prophylaxis is 10-25mg at bedtime, and the therapeutical range is from 10 to 400mg/day [82].

Chronic tension-type headaches (CTTH): CTTH is a disorder that evolves from episodic tension-type headache, with very frequent headache attacks lasting minutes to days. AMI represents the first choice in prophylactic treatment of CTTH supported by the highest levels of evidence [83].

A level A recommendation has been made in favor of using AMI (10-100mg/day) for prophylactic treatment of CTTH following the Strength of Recommendation Taxonomy (SORT) criteria [84]. AMI can achieve improvements in both the headache pattern and Quality of Life (QOL) [85]. AMI can also reduce the suppression of muscle activity and thus help relive headache in CTTH patients [86,87]. Although tricyclic antidepressants, especially AMI, are considered the first line in prophylactic treatment of CTTH, other strategies such as biofeedback, behavioral therapies and relaxation techniques should be taken into consideration [83].

Implications for AMI application

When an AMI therapy is to be started, clinical practitioners have to consider that the dose range is wide and should be individualized. Due to its sedating action, AMI treatment should begin at a low dose (10-25mg is recommended) at bedtime and increased slowly. However, higher doses can be prescribed for patients with comorbidity for depression or anxiety [82]. The adverse effects are the major reasons for low rates of adherence to AMI therapy [88]. The most frequently reported adverse effects include dry mouth, drowsiness and weight gain [82,89]. These side effects are mainly due to the anti-muscarinic and antihistaminic responses, of which the cardiovascular events such as arrythemia belong to the most severe ones. AMI is an contraindication for older patients with hypotension or cardiac disease [90]. Due to less severe sedation (and dry mouth), nortriptyline or desipramine have been preferred over AMI for pain [69,91]. However, comparative studies have not been able to support the advantage of nortriptyline or desipramine over AMI [92-94]. To reduce the adverse effects and promote efficacy, combination of different drugs and different strategies should be taken into consideration [95]. In addition, new drug uses can be an option. For instance, the treatment of neuropathic pain with the topical application of AMI [96].

Conclusion

In summary, the analgesic mechanisms of AMI include inhibition of monoaminergic reuptake, block of sodium ion channels, change of pain-modulation-related receptors, immunological impacts, and improvement of comorbidities. These advancements in knowledge implies that more investigations are needed to further understand other interactions AMI may have. There is a good physiological basis for the use of AMI in chronic pain management and clinical evidence has also confirmed the efficacy of AMI in therapy of neuropathic pain such as PDN and PHN, migraine, CTTH and other chronic pain conditions. However, further studies are still needed to obtain full knowledge of the drug and its best usage.

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