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Review Article

Antimicrobial therapies for chronic pain (part 1): analgesic mechanisms

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ABSTRACT

There is increasing evidence that the relationship between chronic pain and infections is complex and intertwined. Bacterial and viral infections can cause pain through numerous mechanisms such as direct tissue damage and inflammation, the induction of excessive immunologic activity, and the development of peripheral or central sensitization. Treating infections might relieve pain by attenuating these processes, but a growing body of literature suggests that some antimicrobial therapies confer analgesic effects, including for nociceptive and neuropathic pain symptoms, and affective components of pain. The analgesic mechanisms of antimicrobials are indirect, but might be conceptualized into two broad categories: 1) the reduction of the infectious burden and associated pro-inflammatory processes; and 2) the inhibition of signaling processes (*e.g.*, enzymatic and cytokine activity) necessary for nociception and maladaptive neuroplastic changes *via* off-target effects (unintended binding sites). For the former, there is evidence that symptoms of chronic low back pain (when associated with Modic type 1 changes), irritable bowel syndrome, inflammatory bowel disease, chronic pelvic pain, and functional dyspepsia might be improved after antibiotic treatment, though significant questions remain regarding specific regimens and dose, and which subpopulations are most likely to benefit. For the latter, there is evidence that several antimicrobial classes and medications exert analgesic effects independent of their reduction of infectious burden, and these include cephalosporins, ribavirin, chloroquine derivatives, rapalogues, minocycline, dapsone, and piscidin-1. This article aims to comprehensively review the existing literature for antimicrobial agents that have demonstrated analgesic efficacy in preclinical or clinical studies.

Keywords: Analgesia; Anti-Bacterial Agents; Anti-Infective Agents; Antiviral Agents; Central Nervous System Sensitization; Chronic Pain; Infections; Neuralgia; Nociceptive Pain; Pain Management.

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INTRODUCTION

Pain is a cardinal sign of infection, so it stands to reason that antimicrobial agents that treat infection may alleviate pain. Yet, in clinical practice the relationship between pain, infection and antimicrobial agents is more complex. Many individuals whose infection is eradicated may continue to experience chronic pain *via* mechanisms that include autoimmune reactions and peripheral and central sensitization (*e.g.*, Lyme disease, myalgic encephalomyelitis, "long COVID"), in which case antimicrobial treatment may be less effective or ineffective [1]. Low-grade infection may cause neuropathic pain *via* demyelination, neuronal damage, and deafferentation, and predispose to somatic (*e.g.*, discogenic back or neck pain, periodontitis) or visceral nociceptive pain (*e.g.*, some cases of bladder pain syndrome/interstitial cystitis, inflammatory bowel disease [IBD]) through mucosal injury, chronic inflammation, or accelerated degenerative processes [2–5]. Recent evidence also points to variations in gut and other organ system microbiomes as sources of acute pain and chronic neuropathic, nociceptive, or nociplastic pain [6].

All organisms, including humans, share similarities in cellular machinery with microbes, and alterations in the microbiomes of the gut and other organ systems (*e.g.*, respiratory, skin, genitourinary) can have a profound impact on pain. Therefore, the connections among infections, the treatment of infections, and chronic pain are not surprising. Over the past few decades, a growing body of literature has been devoted to these complex relationships [1,4,6], but there has been no systematic attempt to review antimicrobial therapy as a treatment for chronic pain in general, which is more clinically relevant to frontline pain practitioners. The aims of this two-part series are to outline the direct and indirect mechanisms by which antimicrobial therapies can alleviate nociception and pain, categorize the preclinical and clinical evidence supporting antimicrobial therapies in pain conditions, and provide a framework for future directions in this important, but hitherto underrecognized area.

MAIN BODY

1. Search strategy and study selection

The search strategy was the same for parts 1 and 2 of this series. From December 2022 to April 2023, we searched the following databases: PubMed, Embase, and Google Scholar, without language or date restrictions. We cross-referenced the major search terms "chronic pain," "pain," "antimicrobial," "antibiotic," "antiviral," "antifungal," "mechanism," and "infection" with various iterations and subcategories of these keywords to correspond with various pathogens, medications, mechanisms, and chronic pain conditions. We prioritized peer-reviewed pooled analyses (*e.g.*, meta-analyses and systematic reviews) and randomized controlled trials (RCTs), but also included preclinical studies, narrative reviews, case series, and retrospective studies as indicated. In addition to primary sources, we searched reference lists of retrieved articles.

2. Mechanisms of analgesia by antimicrobial agents

The aim of an antimicrobial agent is to eradicate its target pathogen before resistance develops [7]. Bacterial and viral infections can cause pain *via* numerous mechanisms including direct tissue damage, the induction of injurious immune responses, and the development of peripheral or central sensitization [1]. Although some antibiotics and antivirals might cause painful adverse effects (*e.g.*, arthralgia with fluoroquinolones, peripheral neuropathy with antiretroviral therapy) [8], others may confer analgesia in the setting of infections. The analgesic mechanisms of antimicrobials are *via* indirect actions which might be conceptualized into two broad categories (**Fig. 1**): 1) the reduction of infectious burden and associated pro-inflammatory processes; and 2) the inhibition of signaling processes (*e.g.*, enzymatic and cytokine activity) necessary for nociception and maladaptive neuroplastic changes *via* off-target effects (unintended binding sites). Altogether, a variety of acute and chronic pain conditions may be alleviated by antimicrobial agents (**Fig. 2**).

3. Reduction of infectious burden and inflammation

The etiology of Modic type 1 vertebral endplate changes remains controversial, but infection remains one of several plausible causes [9]. Positive cultures (especially for anaerobic microorganisms such as *Propionibacterium acnes*) from biopsies of herniated disc material have been associated with new Modic changes at adjacent vertebrae [10]. In a recent literature review assessing the use of antibiotics for chronic low back pain, Gilligan and colleagues [4] identified only two randomized placebo-controlled trials [11,12]. In the trial by Albert et al. [11], patients with magnetic resonance imaging (MRI) findings of Modic type 1 changes who received 100 days of amoxicillin-clavulanic acid reported statistically significant improve-

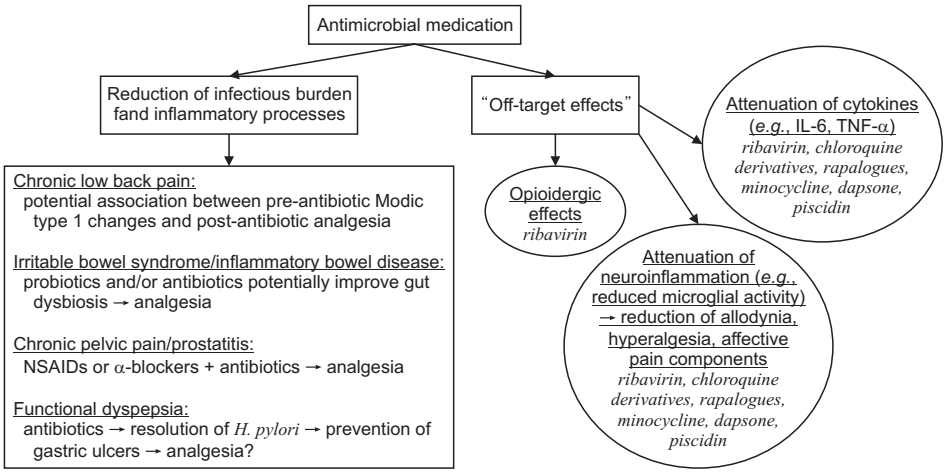

Fig. 1. Indirect analgesic effects of antimicrobial medications. NSAIDs: non-steroidal anti-inflammatory drugs, IL: interleukin, TNF: tumor necrosis factor.

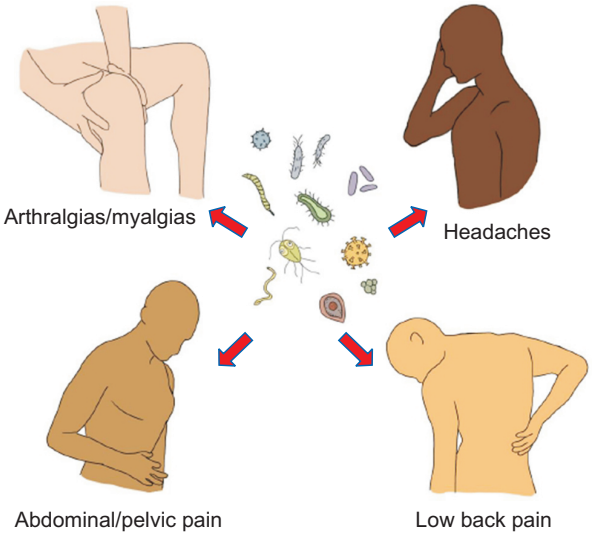

Fig. 2. Artistic rendition illustrating representative acute and chronic pain conditions that may result from infectious processes. Antibacterial, antiviral, and anti-parasitic agents have been found to confer analgesia in each of the following conditions *via* direct effects on pathogen load (*e.g.*, spinal pain, dyspepsia) and/or by off-target effects (*e.g.*, mitigating autoimmune and sensitization processes). Drawing by Seffrah Jin Cohen.

ments in pain and function. Patients in the antibiotic group also had a greater likelihood of MRI-confirmed resolution of their Modic changes. However, in the trial by Bråten et al. [12], patients with MRI-confirmed Modic type 1 or type 2 changes reported no benefit in pain or functional outcomes after 100 days of amoxicillin, though post-intervention MRIs were not assessed. Given this limited and mixed evidence, it is uncertain whether antibiotics can reliably treat pain in the context of Modic type 1 changes, which might be associated with low-grade infection, pro-inflammatory processes, or both [9,10]. Nonetheless, the association between Modic type 1 resolution and analgesia with antibiotic use suggests that the reduction of microbial and pro-inflammatory burden is a potential mechanism.

A meta-analysis of patients with irritable bowel syndrome (IBS) found potential benefit for probiotics and rifaximin for abdominal pain symptoms *via* potential alterations to the gut microbiota, but high heterogeneity among the included studies precluded estimates of effect size [13]. A systematic review of patients with IBD also found analgesic benefit from antibiotics by treating small bowel bacterial overgrowth [14], although the data for this conclusion were based on one RCT [15]. A meta-analysis of patients with chronic prostatitis/chronic pelvic pain syndrome found that antibiotics (*e.g.*, fluoroquinolones) and non-steroidal anti-inflammatory drugs reduced pain scores compared to a placebo, with a combination of α-blockers and antibiotics being the most efficacious regimen for analgesia [16].

In functional dyspepsia, although a meta-analysis of patients with known *Helicobacter pylori* infection failed to identify short-term (< 1 year) symptomatic improvement with antibiotics, there was significant improvement noted on long-term (≥ 1 year) follow-up [17]. These deferred benefits might be attributable to a greater likelihood of antibiotic-treated patients to have histologic resolution of chronic gastritis and the prevention of peptic ulcer disease [17]. In one placebo-controlled RCT that excluded patients with *H. pylori*, rifaximin significantly reduced dyspeptic symptoms, though follow-up was limited to only 8 weeks and the putative mechanism (alteration of the duodenal microbiota) has yet to be confirmed [18]. The precise relationship between *H. pylori* and func-

tional dyspepsia remains unclear. *H. pylori* is recognized as an organic cause of dyspeptic symptoms, but consensus guidelines have suggested with some controversy [19] that functional dyspepsia is a specific diagnosis that is distinct from *H. pylori*-associated dyspepsia [20] and better reserved for describing symptoms that persist despite successful antibiotic treatment.

In summary, when microbiome dysbiosis (*e.g.*, IBS) or an active infection (whether symptomatic or subclinical) potentially mediates pain symptoms, antibiotics might confer analgesia by reducing pathogen burden or altering microbiome compositions, leading to the attenuation of further tissue injury and pro-inflammatory processes. The available evidence is limited, and more studies are needed to assess how strongly analgesia is associated with radiologic or histologic evidence of infection eradication.

4. Inhibition of nociception and pain signaling *via* off-target effects

Antimicrobials can confer analgesia *via* mechanisms independent of reducing infectious burden and associated inflammation. Several antimicrobial agents are known to inhibit enzymes, proteins, or neurotransmitters necessary for pain signaling (*e.g.*, protein kinase expression, pro-inflammatory cytokine activity) and maladaptive neuroplastic changes (*e.g.*, dorsal horn remodeling, induction of hyperalgesia). These disruptions to pain processing are generally the consequence of unintended binding sites, and may be described as beneficial off-target effects [21]. Antimicrobial agents with known off-target analgesic effects are summarized below and in **Table 1**. It is important to note that because analgesia is not the primary therapeutic intent for antimicrobials, relatively few studies specifically assess the effect of antimicrobials on nociception, and this relationship might be underrecognized.

1) Cephalosporins

Cephalosporins are beta-lactam antimicrobials first discovered and isolated from the mold *Cephalosporin acremonium* (also named *Acremonium chrysogenum*) in 1945, and have since become one of the most prescribed antibiotics [22]. Five generations of cephalosporins have been developed and are collectively utilized against a variety of gram-positive and gram-negative bacteria. Cephalosporins exert bactericidal activity *via* their beta-lactam rings, which inhibit penicillin-binding proteins essential for bacterial cell wall synthesis [23].

In preclinical studies, there is evidence that ceftriaxone increases the expression of glial glutamate transporter-1 (GLT-1), which might confer neuroprotective effects by preventing neurotoxicity from excessive glutamate levels [24]. In a murine chronic constriction injury (CCI) model, hyperalgesia and allodynia were associated with downregulation of GLT-1 in the spinal dorsal horn; when intraperitoneal or intrathecal ceftriaxone was administered, GLT-1 expression and glutamate uptake increased, and thermal hyperalgesia and mechanical allodynia were reversed [25]. Moreover, when a GLT-1 inhibitor was administered following ceftriaxone administration, these beneficial effects were blunted [25]. In another murine study comparing the effects of ceftriaxone and gabapentin on neuropathic pain, both medications produced a similar effect size on the reduction of allodynia and hyperalgesia [26]. Ceftriaxone might also inhibit pro-inflammatory cytokine production (*e.g.*, tumor necrosis factor [TNF]-α, interleukin [IL]-1β) in response to neuropathic injury [27], potentially *via* a poorly understood relationship between GLT-1 and inflammatory mediators [28].

Limited clinical data exist pertaining to cephalosporins and analgesia. In one case report, cephalexin following a course of minocycline provided a near-resolution of spasticity and pain in a patient with neurosarcoidosis [29]. In one comparative-effectiveness trial in 45 patients undergoing median or ulnar nerve decompression, participants were randomized to receive a single pre-incisional infusion of saline, saline with ceftriaxone (2 grams), or saline with cefazolin (2 grams). The patients in the ceftriaxone group reported a significant increase in pain thresholds up to 6 hours after surgery, whereas the patients in the other groups reported no significant difference [30]. The same investigators also tested a murine model of postsurgical pain, and the mice that received intraperitoneal ceftriaxone had greater dorsal horn GLT-1 expression and a greater reduction in nocifensive behavior than those that received saline or cefazolin [30]. This study did not evaluate why cefazolin, also a cephalosporin, appeared to lack analgesic efficacy. Although cefazolin is a first-generation cephalosporin whereas ceftriaxone is a third-generation cephalosporin [23], cefazolin has also demonstrated the ability to upregulate GLT-1 expression [31]. Further studies are needed to clarify whether the different generations of cephalosporins involve differential analgesic mechanisms or confer varying levels of analgesia.

Table 1. Summary of the evidence for antimicrobial agents with possible off-target analgesic effects

Antimicrobial agent	Mechanism(s) of action	Preclinical evidence for antinociception	Clinical evidence for a therapeutic effect
Cephalosporins [24,27]	Upregulation of glial glutamate transporter-1, preventing glutamate neurotoxicity and potentially reducing pro-inflammatory cytokine concentrations.	Evidence for neuroprotection in neurodegenerative diseases (*e.g.*, amyotrophic lateral sclerosis) and the prevention or treatment of neuropathic pain.	Ceftriaxone possibly mitigates post-surgical pain. Only specific cephalosporins, or specific generations of cephalosporins, might confer analgesic effects, but this requires confirmation.
Ribavirin [34,61]	Possibly competitive inhibition of inosine monophosphate dehydrogenase, increasing the frequency of deleterious viral mutations. Partial reversal by naloxone suggests opioidergic effects.	Evidence for antinociception in models of acute inflammatory pain. Effect partially reversed by naloxone and enhanced by propranolol, baclofen, ibuprofen, and others.	Scant evidence for benefit compared to standard analgesics for viral-associated (*e.g.*, chikungunya) joint pain.
Hydroxychloroquine, Chloroquine [40,50,61,65]	Antirheumatic effects may result from interference with "antigen processing" in macrophages and other cells, and inhibition of autophagy.	Evidence for complex regional pain syndrome and numerous inflammatory disorders and neoplastic diseases.	No evidence for benefit compared to placebo or standard analgesics for viral-associated joint pain. Less efficacious than other disease-modifying agents for rheumatoid arthritis but may provide value as add-on therapy. Low-level evidence for other inflammatory diseases (*e.g.*, lupus, dermatomyositis). Anecdotal evidence for complex regional pain syndrome.
Rapamycin [73,91]	Inhibits mammalian target of rapamycin complex 1 (mTOR) and inhibits synaptic plasticity.	Evidence for neuropathic pain, opioid-induced hyperalgesia, central sensitization, affective components of pain, inflammatory myopathies, mitochondrial disorders, and cancer-associated pain.	Evidence for anti-tumor effects and cancer-associated pain. Anecdotal evidence in genetic heterotopic ossification and inflammatory myopathies.
Minocycline [99,102–104,107,120,125,128]	Inhibits central and peripheral glial cell activity, attenuates release of inflammatory cytokines, and binds to NR2B subunit of N-methyl-D-aspartate receptors.	Evidence for neuropathic (*e.g.*, painful diabetic neuropathy) and nociceptive (*e.g.*, visceral) pain conditions and cancer-associated bone pain. May reduce affective components of pain, such as depression, anxiety, and fear.	No benefit compared to placebo or tricyclic antidepressants for lumbar radicular pain. Potential benefit for peripheral neuropathic conditions in small prospective studies.
Dapsone [142,143]	Inhibition of neutrophil activity and release of inflammatory cytokines.	Evidence for inflammatory disorders. May cause neuropathy and hemolysis with prolonged use.	Superior to placebo for rheumatoid arthritis, comparable to chloroquines. Anecdotal evidence for bullous systemic lupus erythematosus and several inflammatory dermatoses.
Piscidin-1 [173,174]	Glial cell inhibition, suppression of cyclooxygenase-2 and inducible nitric oxide synthase.	Evidence for neuropathic pain and tumor apoptosis.	Clinical evidence is lacking.

2) Ribavirin

Ribavirin is a guanosine analog that is used to treat respiratory syncytial virus and Lassa virus, but is perhaps most recognized as a treatment for chronic hepatitis C when co-administered with interferon-alpha [32]. Ribavirin has several putative mechanisms of action, such as facilitating viral RNA chain termination, increasing the sensitivity of target cells to interferon, and inhibiting viral enzymes (*e.g.*, inosine monophosphate dehydrogenase) necessary for energy production or genetic replication [32–34].

In one murine study, ribavirin decreased nociceptive responses to noxious stimuli (*e.g.*, formalin, capsaicin) and provided analgesia for visceral pain (*e.g.*, intra-abdominal acetic acid injections) [34]. Because these analgesic effects were attenuated with the administration of naloxone and enhanced with dopamine D2 receptor activity (regardless of agonism or antagonism), endogenous opioid or dopaminergic pathways might be involved, though the exact mechanisms remain uncertain [34]. In two other murine studies, ribavirin reduced histologic signs of neuroinflammation, such as microglial infiltration and demyelination [35], as well as astrocyte proliferation and glial scarring [36]. Ribavirin has also demonstrated the ability to reduce levels of pro-inflammatory cytokines (*e.g.*, IL-1β, IL-6, and TNF-α) [37], but the degree to which this confers analgesia remains unclear.

Although ribavirin is not widely used for the purpose of analgesia, at least one proprietary medication using ribavirin has been developed and tested in a peripheral nerve injury mouse model, which appeared to facilitate axonal regeneration and increase thresholds for hyperalgesia and allodynia [38].

3) Chloroquine derivatives

Chloroquine and hydroxychloroquine are antimalarial medications used as disease-modifying antirheumatic drugs (DMARDs) in several autoimmune conditions, such as systemic lupus erythematosus (SLE) [39] and rheumatoid arthritis (RA) [40], though more recent guidelines [41] have deemphasized the use of hydroxychloroquine as monotherapy or a first-line DMARD in RA due to concerns of modest benefits and substantial risks of adverse effects (*e.g.*, nausea and vomiting [42], myopathy [43], retinopathy [44]). Chloroquine derivatives inhibit lysosomes [45] and several pathways in the immune cascade, including Toll-like receptor (TLR) activity [46], pro-inflammatory cytokine production (*e.g.*, IL-1, TNF) [47], and T-cell antigen presentation [48]. The inhibition of lysosomal and T-cell activity, in conjunction with the reduction of TLR and proinflammatory cytokine signaling, is likely the means through which autoimmune activation and associated tissue injury is attenuated, but the mechanisms of action for chloroquine derivatives are numerous and incompletely understood [49]. Although outside the scope of this review, the immunologic (*e.g.,* inhibition of autophagy) and anti-inflammatory effects of chloroquine derivatives might inhibit tumor growth and increase the efficacy of chemotherapy drugs [50].

The numerous immunomodulatory and anti-inflammatory effects of chloroquine derivatives provide a mechanistic basis for conferring analgesia. Additionally, murine studies have demonstrated a local anesthetic effect when chloroquines are administered intrathecally [51] or subcutaneously [52,53], possibly *via* their ability to antagonize potassium, sodium, and calcium channels [54]. However, clinical studies have mostly been negative, with large multicenter RCTs in osteoarthritis hand pain demonstrating no benefit of hydroxychloroquine over placebo [55,56]. Similarly, a recent cost-utility analysis found that hydroxychloroquine does not provide cost-effective benefits for pain and quality of life in hand osteoarthritis [57]. Although early data suggested that hydroxychloroquine might benefit arthritis pain in the context of SLE [58], a large placebo-controlled multicenter RCT demonstrated no benefit for hydroxychloroquine in inflammatory arthritis pain [59]. A systematic review of treatments for chikungunya virus-associated pain found that chloroquine was superior to placebo for chronic pain, though not for acute pain, with only five trials comprising 402 total patients included [60]. A more recent systematic review that included 11 studies pertaining to chikungunya-associated joint pain found no benefit from chloroquine or hydroxychloroquine compared to placebo [61].

Smaller studies continue to suggest that chloroquine derivatives might be of benefit in other pain syndromes with potential autoimmune-mediated mechanisms. Two case series of oral lichen planus [62,63] and a retrospective analysis in perineal lichen planus [64] suggest that hydroxychloroquine might facilitate the healing of painful erosions, but prospective placebo-controlled trials have yet to be completed. A small case series in seven patients with complex regional pain syndrome (CRPS) combined with a CRPS murine model demonstrated a decrease in self-reported pain scores with daily hydroxychloroquine, and reduced spinal cord dorsal horn microglial and cytokine activity in the mice [65]. Allodynia, paw edema, and temperature discrepancies (signs associated with CRPS) were also decreased in the mice receiving hydroxychloro-

quine, suggesting a reduction in neuroinflammation [65].

Although chloroquine derivatives do not appear to confer a large magnitude of analgesia, and controlled studies and pooled analyses have so far been negative, their inhibition of numerous inflammatory and immunologic processes involved with pain signaling is well-described. It is possible that the pain mechanisms (and pain diagnoses) most amenable to treatment from chloroquine derivatives have simply yet to be clarified.

4) Rapamycin (sirolimus) and rapalogues

Rapamycin (sirolimus) is a macrolide produced by the bacteria *Streptomyces hygroscopicus* that was initially utilized for its antifungal and immunosuppressive properties [66,67]. The molecular target of rapamycin was identified as a protein kinase that regulates intracellular anabolic and catabolic signaling in mammals, and this kinase was subsequently named "mTOR" (initially an abbreviation for "mammalian target of rapamycin," later revised to "mechanistic target of rapamycin") [67].

The mTOR kinase is a component of numerous intracellular functions and is implicated in various diseases. The inhibition of mTOR by rapamycin or its analogues ("rapalogues") has been studied as a treatment strategy for various cancers [68,69] (*e.g.*, pancreatic [70], renal cell [71]), myopathies (*e.g.*, mitochondrial myopathy [72], inflammatory myopathy [73], inclusion body myositis [74]), sickle cell disease [75], fragile X syndrome [76], viral prophylaxis for transplant recipients [77], and possible anti-aging effects [78,79].

Rapalogue inhibition of mTOR disrupts several maladaptive processes associated with the chronification of pain. In murine neuropathic pain models, intrathecal [80,81] or intraperitoneal [82,83] rapamycin inhibits astrocyte and microglial cell activation, as well as levels of pro-inflammatory neuropeptides including calcitonin gene-related peptide, substance P, and several cytokines (*e.g.*, IL-1β, IL-6, TNF-α [83]). Significant mTOR activity has been identified in the insular cortex, dorsal root ganglia, and laminae I–III of the dorsal horn in murine studies [84–86], with mTOR blockade by rapalogues attenuating wind-up and mechanically-evoked potentials [85], thereby reducing allodynia [84], increasing the activation thresholds of nociceptive Aδ fibers [86], and inhibiting hyperalgesic priming [87]. There is also data supporting the role of mTOR in mediating affective components of pain, with murine models demonstrating improvement of pain behaviors with mTOR blockade [88,89].

It is noteworthy that mTOR upregulates intracellular signaling pathways (*e.g.*, PI3K/Akt/mTOR) and the expression of protein kinases (*e.g.*, PKCγ, neuronal NOS) associated with opioid-induced tolerance and opioid-induced hyperalgesia (OIH) [90,91]. In murine models, rapamycin and other mTOR inhibitors (*e.g.*, metformin) have shown efficacy for reducing morphine tolerance and hyperalgesia [90,92,93]. The use of rapalogues for treating opioid-induced tolerance and OIH has not been described in a clinical setting, but their utility for this purpose might be limited by potentially serious adverse effects associated with mTOR inhibition (*e.g.*, metabolic dysfunction, anemia, renal failure [94]).

5) Minocycline

Minocycline is a second-generation tetracycline that has demonstrated the ability to reduce neuroinflammation, neuropathic pain, and nociceptive pain in preclinical studies [95] *via* mechanisms independent of its antimicrobial effects [96,97]. Minocycline inhibits central [98–101] and peripheral [102,103] glial cell activity and attenuates the release of pro-inflammatory cytokines such as IL-1β [104,105] and TNF [106]. There is limited data suggesting that minocycline might also confer analgesia by binding to the NR2B subunit of N-methyl-D-aspartate (NMDA) receptors [107]. Because minocycline crosses the blood-brain barrier, recent focus has been on its potential neuroprotective effects [108,109], but clinical efficacy for this indication remains uncertain [110].

Numerous murine studies have demonstrated analgesic benefit in a variety of mechanistic pain categories, including neuropathic pain (*e.g.*, mechanical allodynia and hyperalgesia [105,111,112], chemotherapy-induced peripheral neuropathy [CIPN] [113,114], and painful diabetic neuropathy [107,115–117]), nociceptive pain [96,97,118,119] (including visceral pain [120–122]), and mixed pain conditions (*e.g.*, endotoxin-induced hyperalgesia and arthralgia [123], and cancer-associated bone pain [124,125]). Minocycline potentially improves affective components of pain, such as depression, anxiety, and fear [126–128], and older studies suggested that minocycline might also prevent the development of opioid tolerance *via* glutaminergic or anti-microglial mechanisms [129,130].

However, clinical studies are few and have shown mixed results. A recent literature review identified only nine prospective trials assessing the analgesic efficacy of minocycline [131]. Three small RCTs [132–134] studied the use of minocycline for CIPN, with only one [134] demonstrating clinically meaningful benefit. Two RCTs

[135,136] assessed the efficacy of minocycline for lumbar radicular pain, and there was no significant benefit over a placebo [135] or amitriptyline [136]. One RCT of 50 participants found benefit for painful diabetic neuropathy symptoms [137], and in a small pilot study in patients with leprosy-associated neuropathy, 9 of 11 participants reported improvements in sensory and motor function tests [138]. Minocycline did not accelerate the resolution of postsurgical symptoms after hand surgery in an RCT of 131 patients [139] and did not yield clinically meaningful analgesia in a small open-label trial of 20 patients with neuropathic pain from heterogeneous etiologies (*e.g.*, phantom limb pain, CIPN, and brachial plexopathy) [128]. Although minocycline appears to be safe [131], headaches and vestibular symptoms are common [140], and more studies are necessary to demonstrate whether minocycline has clinical utility for analgesia.

6) Dapsone

Dapsone is a sulfonamide antibiotic that was initially synthesized in 1908 [141] and has both antimicrobial and anti-inflammatory properties [142]. Dapsone is bacteriostatic rather than bactericidal [141], and impedes bacterial replication by inhibiting dihydrofolic acid synthesis [143]. Numerous potential anti-inflammatory mechanisms for dapsone have been proposed [141], such as the inhibition of reactive oxidants and proteases [144], attenuation of mast cell activity [145], and the suppression of pro-inflammatory cytokines (*e.g.*, IL-8 [146] and TNF-α [147]). Although dapsone has been a treatment for leprosy and malaria for decades [142], recent interest has focused on its utility for non-infectious, inflammatory dermatologic conditions (*e.g.*, dermatitis herpetiformis) [141,143].

Murine models have provided evidence for a neuroprotective effect from dapsone, which might have relevance for neurodegenerative and neuropathic pain conditions. Dapsone has demonstrated the ability to attenuate the development of striatal necrosis [148] and the depletion of gamma-aminobutyric acid levels [149] after the injection of quinolinic acid, a neurotoxic NMDA receptor agonist. Dapsone might prevent excessive lipid peroxidation [148] or glutamate agonism [149], which was corroborated by a spinal cord injury (SCI) murine model in which dapsone appeared to antagonize lipid peroxidase and normalize glutathione concentrations [150]. Notably, tactile allodynia and mechanical hyperalgesia were similarly improved with either early (3 hours post-injury) or delayed administration (15 days post-injury) of dapsone [150]. Other SCI murine models have shown that dapsone can improve neurological function by reducing cell apoptosis [151] and inhibiting myeloperoxidase [152], limiting the extent of neurological tissue damage. The evidence for dapsone's effects on the peripheral nervous system is limited, but it appears to similarly inhibit proinflammatory cytokines and maintain glutathione activity, improving thermal and mechanical pain thresholds in a CIPN murine model [153].

Clinical studies have used dapsone for nociceptive pain conditions rather than for neuropathic pain. A placebo-controlled trial [154] and two small comparative-effectiveness trials pitting dapsone against chloroquine derivatives [155,156] found dapsone to be superior to a placebo but not chloroquine in reducing inflammatory biomarkers and pain in RA. Hemolysis and hemolytic anemia were adverse events in all three studies, demonstrating a relatively poor risk-to-benefit profile. These studies were completed several decades ago and newer studies have not re-assessed the efficacy of dapsone for arthritis pain. More recently, dapsone has been recognized for its efficacy in neutrophilic urticarial dermatosis [157] and cutaneous lupus erythematosus (CLE) [158,159], with case reports demonstrating significant benefit in subtypes including lupus erythematosus profundus [160] and bullous lupus erythematosus [161]. Although more placebo-controlled or comparative-effectiveness studies are needed, dapsone is now recognized as a second-line therapy in CLE treatment guidelines [162].

Given its antioxidant and antiapoptotic properties, dapsone has also demonstrated efficacy in animal models and controlled and uncontrolled human studies for neurodegenerative diseases frequently associated with central neuropathic pain and spasticity, such as Parkinson's disease, Alzheimer's disease, stroke, and epilepsy [163–165]. Whereas these studies have not focused on pain as a primary outcome, given the correlation between disease burden and pain symptoms for these conditions, future studies evaluating dapsone should consider assessing pain and related quality of life measures.

It is important to recognize that dapsone is used in inflammatory dermatoses primarily for its immunomodulating and disease-modifying effects [166] rather than for analgesia. In addition to hemolysis, chronic dapsone use is associated with peripheral neuropathy [167] (potentially *via* paradoxical axonal toxicity [168]), methemoglobinemia, agranulocytosis, and dapsone hypersensitivity syndrome [142], a condition that can lead to fatal liver dysfunction [169]. Although dapsone can be safely used, its significant risks of toxicity require regular serum mon-

itoring and likely preclude its use as an analgesic medication.

7) Piscidin-1

Piscidin is an antimicrobial peptide named for its natural occurrence in the skin and gills of various fish species [170]. Piscidin is produced in mucosal and epithelial cells [171] as well as mast cells and eosinophils [170], and likely plays an important role in the immune systems of fish by preventing microbial colonization of the skin. While at least seven piscidin isoforms have been identified, all of which have antimicrobial and immunological functions [172], only piscidin-1 (PCD-1) has been reported to have analgesic properties [173].

In a murine CCI model, PCD-1 was found to inhibit the upregulation of inducible nitric oxide synthase and cyclooxygenase-2 in response to lipopolysaccharide antigen, which suggests potential efficacy for nociceptive pain symptoms [173]. In addition, PCD-1 improved thermal hyperalgesia (increased paw withdrawal latency) at a magnitude of effect similar to that of gabapentin and increased paw withdrawal thresholds (*e.g.*, mechanical allodynia). Immunohistologic examination also demonstrated decreased dorsal horn microglial activity in the CCI rats that had been treated with PCD-1 compared to those in the control group [173]. In preclinical studies, PCD-1 facilitates mitochondrial dysfunction and apoptosis in osteosarcoma cells [174], and piscidin-4 induces tumor necrosis in triple-negative breast cancer cells [175].

No clinical studies to date have assessed the analgesic effects of PCD-1, and there is a lack of additional preclinical studies confirming potential mechanisms. Given the limited but encouraging data available suggesting efficacy for nociceptive pain, neuropathic pain, and certain cancers, further study of PCD-1 and other piscidin isoforms is warranted.

5. Future research

The analgesic effects of many medications (*e.g.*, antidepressants) besides antimicrobial agents have been discovered serendipitously, and the exploration of these off-target effects in the quest to develop antimicrobial agents has led to the development of medications used for non-infectious conditions that share significant overlap with chronic pain (*e.g.*, meprobamate for anxiety and sleep disorders, chlorpromazine for sleep, anxiety and psychosis) [176]. However, there are several unique challenges in repurposing antimicrobial agents for analgesic and other purposes, including antibiotic stewardship (*e.g.*, preventing future resistance in non-infected individuals) and unintended effects on the microbiome, which can have myriad unintended effects on the development of chronic pain conditions [6].

Identifying mechanisms requires preclinical studies, of which a substantial proportion (greater than 50% in some estimates) involves indirect-acting mechanisms such as phages or phage-derived peptides, virulence factors, antibiotic-drug conjugates, microbiome-modulating therapies, immunomodulators, drug potentiators, and a host of other non-traditional targets [177]. Unique characteristics that undermine translation from animals to humans for antimicrobial therapy and pain should be addressed. For the former, these include differences in antimicrobial effectiveness between preclinical and clinical contexts, differences in genomics, proteomics and metabolism between species, the need for evaluating disease-modulating properties which typically take longer to realize than detecting reductions in microbial populations, and difficulties in detecting long-term cytotoxic effects in non-humans, amongst others. For the latter, they might include finding ways to concomitantly measure the effects of therapy on nociception (for neuropathic and non-neuropathic pain) and antimicrobial activity, and the inherent difficulties outlined elsewhere in translating preclinical pain studies to humans. These include differences in the physiological properties of nociception and the subjective phenomenon of pain that includes affective and cognitive components, designing studies that account for the diversity of humans including vulnerable populations often excluded from clinical trials, and addressing common design flaws such as blinding, randomization, and small sample sizes which may fail to detect modest signals for analgesic properties [178].

CONCLUSIONS

Antimicrobials are not expected to have mechanistic effects on several key processes implicated in the initiation and propagation of chronic pain syndromes, many of which are autoimmune-mediated (*e.g.*, epitope spreading, molecular mimicry) [1]. Moreover, antimicrobials cannot reverse tissue or nerve damage that has already occurred from infection (*e.g.*, vaccination remains the best intervention to prevent postherpetic neuralgia [179]). Antimicrobials should be used judiciously, and should not be utilized to treat pain conditions when there is no physiologic or mechanistic basis for efficacy. Nonethe-

less, antimicrobials have shown surprising analgesic effects, including *via* numerous off-target effects on pain signaling. These mechanisms require further investigation in order to optimize any potential analgesic benefits and to understand which patient populations may most likely benefit.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed for this paper.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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