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Review

Neuronal and immunological basis of action of antidepressants in chronic pain – clinical and experimental studies

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Abstract:
The current knowledge of the pharmacological actions of the tricyclic antidepressants (TCAs) has slowly evolved through their over 40-year history. Chronic pain represents one of the most important public health problems, and antidepressants are an essential part of the therapeutic strategy in addition to classical analgesics. This article reviews the available evidence on the efficacy and safety of antidepressants in chronic pain conditions; namely, headaches, low back pain, fibromyalgia, cancer pain and especially neuropathic pain. TCAs are traditionally the main type of depression medication used to treat chronic pain. Recently, new antidepressants were introduced into clinical use, with a significant reduction in side effects and equivalent efficacy on mood disorders. These new drugs that are effective for chronic pain belong to the tetracyclic antidepressants (TeCAs) group (amoxapine, maprotiline), the serotonin and noradrenaline reuptake inhibitors (SNRIs) group (duloxetine, venlafaxine, milnacipran) and the atypical antidepressants group (bupropion, trazodone, mirtazapine, nefazodone). In this review, we present the available publications on TCAs (amitriptyline, doxepin, imipramine, desipramine, nortriptyline), TeCAs (amoxapine, maprotiline), selective serotonin reuptake inhibitors (SSRIs) (citalopram, fluoxetine, paroxetine), SNRIs (duloxetine, venlafaxine, milnacipran) and atypical antidepressants (bupropion) for the treatment of neuropathic pain. We also review analgesics acting as both opioid receptor agonists and also acting as aminergic reuptake inhibitors. Existing data are insufficient to conclude which of these new classes of antidepressants has the best clinical profile and will be the most effective in the treatment of neuropathic pain; in addition, a lower incidence of side effects should be considered. Increased experimental and translational research is a key for further improvement of the treatment of chronic pain with antidepressants. However, evidence from basic science is needed to improve our understanding of the mechanisms of action and their possible pharmacodynamic interactions.

Key words:
antidepressants, chronic pain, neuropathy

Introduction

Chronic pain develops as a consequence of injury or pathology affecting the somatosensory pathways in the peripheral or central nervous system (CNS). Pain stimulus that originates in the periphery is transported by primary sensory neurons through the dorsal horn of the spinal cord and then to many brain structures throughout the ascending pain pathway. In the spinal cord, the descending fibres originating in the brainstem suppress pain neurotransmission; this suppression functions as a homeostatic regulator. The neurotransmitters released by the descending fibres are se-

rotonin and noradrenaline, and dysfunction of these systems is likely to induce dysfunctional descending serotonin or noradrenaline antinociceptive pathways, which explains comorbid pain symptoms in some patients with depression [37]. Patients with chronic pain are prone to depression in addition to a continuous load of the disease-intensified pain. Because of the shared nature of depression and pain, the presence of both conditions in a patient may lead to similar therapies. The most universally used antidepressants for chronic pain are tricyclic antidepressants (TCAs); however, selective serotonin or noradrenaline reuptake inhibitors and a few other antidepressants are also effective against pain. People respond differently to depression medications because each chronic pain condition is unique. Antidepressants are commonly used to treat the following chronic pain conditions: arthritis, central pain syndrome, fibromyalgia, low back pain, migraines, nerve damage from diabetes (diabetic neuropathy), and nerve damage from shingles (postherpetic neuralgia). Their effectiveness is the best documented for painful diabetic neuropathy and herpetic neuralgia. On the other hand, some clinical data suggest that in patients with depression but without pain symptoms after prolonged use of amitriptyline the headache can occur [52], and in contrast, we found pronociceptive effect in naive animals after peripheral injection of doxepine and amitriptyline [in preparation]. These observations mean that in the absence of pathological changes associated with depression or chronic pain effects of antidepressant drugs may change its character to pronociceptive. The explanation of this phenomenon requires further research.

The analgesic potency of antidepressant drugs has been suggested to result from the inhibition of monoamine reuptake in the CNS, which consequentially leads to increased activity of the antinociceptive descending pathways.

The antidepressants have an analgesic effect that may be, at least partly, independent of their effect on depression. The dose at which it is necessary to administer them in order to achieve optimal analgesia is usually lower than that which is required for antidepressant therapy [18], which may suggest separation of analgesic and antidepressant effect. Another confirmation of this thesis may be the differences in analgesic effectiveness between different classes of antidepressants [33] as well as the fact that the delay in onset of analgesic effects after administration appears after shorter time than antidepressant effect [20]. Amitriptyline, nortriptyline and desipramine have been established as analgesics independent of their antidepressant effects [16]. However, other mechanisms have been suggested. For example, amitriptyline has been found to block N-methyl-D-aspartate (NMDA) receptors, to interact directly with opioids receptors, to act as a sodium channel blocker and to inhibit the cellular uptake of adenosine, which consequentially activates adenosine A_1 receptors on sensory nerve terminals. Several recently published papers have considered a neuroimmune influence on the pain-relieving mechanisms of antidepressants. Accumulated evidence demonstrated that spinal glial cells and their immune factors play an important role in persistent pain development [34, 56]. Some proinflammatory cytokines, such as IL-6 and IL-1β derived from activated glia, are common mediators of pain [35, 56]. However, it is still unclear which type of glial cells plays the most significant role in chronic pain development and how antidepressants affect these cells. Zhu et al. [61] reported that mirtazapine markedly reduced hippocampal cytokine production and glial activation, which was blocked by both serotonergic and adrenergic antagonists. The new approaches to the treatment of chronic, especially neuropathic, pain are based on the more comprehensive knowledge of the interaction between neuronal, glial and immune cells. Up to now, only a few studies on neuroimmune influence in the pain-relieving mechanisms of antidepressants have been carried out. The question has been posed as to which of the antidepressants has the best clinical profile and could be most effective in the treatment of chronic pain and especially neuropathic pain, which is known to be related to changes in neuroimmune interactions.

Classification of antidepressants and their use in the treatment of chronic pain (Tab. 1)

Tricyclic and tetracyclic antidepressants (TCAs and TeCAs)

The TCAs were first discovered at the beginning of the 1950s and consequently introduced later in the decade. They are named after their chemical structure,

Tab. 1. Primary mechanism of antidepressants effective for chronic pain

Groups	Drugs	Mechanisms
TCA	Amitriptyline Doxepin Imipramine	5-HT > NE reuptake inhibition
	Desipramine Nortriptyline	NE 5-HT reuptake inhibition
TeCA	Amoxapine	NE and 5-HT reuptake inhibition
	Maprotiline	NE 5-HT DA reuptake inhibition blocking receptors: H_1; 5-HT_2, α_1-NE, D_2, mACh
SSRI	Citalopram Fluoxetine Paroxetine Sertraline Fluvoxamine	5-HT > NE reuptake inhibition
SNRI	Duloxetine Venlafaxine Milnacipran	5-HT NE > DA reuptake inhibition
MAOI	–	–
Atypical antidepressant	Bupropion	DA NE reuptake inhibition
	Trazodone	5-HT_2 receptor blockade 5-HT reuptake inhibition
	Mirtazapine	α_2-NE and 5-HT_2 presynaptic agonist; 5-$HT_{2/3}$ receptor blockade
	Nefazodone	5-HT_2 receptor blockade 5-HT reuptake inhibition

which contains three rings of atoms. The TeCAs, which contain four rings of atoms, are a closely related group of antidepressant compounds. These older antidepressants are effective but are usually not a first-choice treatment for depression because of their numerous side effects, such as constipation, sedation, dry mouth, difficulty urinating, weight gain and sexual side effects. It is now becoming apparent that TCAs can have an analgesic effect when applied topically and that this effect is produced by peripheral mechanisms rather than systemic uptake. In some cases, a low dose of a cyclic antidepressant may be added to another antidepressant, such as an selective serotonin reuptake inhibitor (SSRI), to increase the antidepressant effect [13]. These medications are not usually given to older adults or people who have low blood pressure or certain heart problems. Some TCAs also have sedative properties, which may help regulate sleep.

In addition, TCAs and TeCAs are traditionally the main type of depression medication used to treat chronic pain. Some of the most common forms of chronic pain therapy are based on TCAs (amitriptyline, nortriptyline, desipramine, imipramine, doxepin, trimipramine, clomipramine and protriptyline) and on TeCAs (amoxapine and maprotiline). The TCAs and/or TeCAs can influence analgesia by a number of different mechanisms: the serotonergic system can be affected by interference of serotonin reuptake and alteration of serotonin binding to receptors; the noradrenergic system can be affected by interaction with α_2-adrenoreceptors; the opioidergic system can be affected by modification of opioid receptor densities in several brain structures; $GABA_B$ receptors can be affected by an increase of receptor function; glutamate receptors can be affected by binding to NMDA and/or AMPA receptors; and adenosine receptors can be affected by inhibition of adenosine uptake peripherally, especially by A_1 receptor activation. Other receptors can also be affected by mechanisms, such as inhibition of histaminergic, cholinergic, muscarinic and nicotinic receptors, blocking or activating voltage-dependent sodium, calcium or potassium channels, and by inhibition of inflammation by decreased prostaglandin E_2 and tumor necrosis factor α production [9, 15, 21, 32]. In 2005, Sindrup et al. [48] reported that the TCAs and TeCAs have no effect on dopamine reuptake, but they might have some indirect dopaminergic action by the adrenergic effect and desensitization of dopamine D_2 receptors. The classical TCAs differ in their effect on monoamine reuptake. Amitriptyline, imipramine and clomipramine cause a balanced inhibition of serotonin and noradrenaline reuptake *in vivo*. The serotonin reuptake inhibition is exerted by the compounds themselves, whereas the noradrenaline reuptake inhibition comes from their respective metabolites, nortriptyline, desipramine and desmethylclomipramine.

It is well documented that TCAs relieve chronic pain:

• **Amitriptyline** has been a first-line treatment for chronic pain for many years. Many studies suggest that amitriptyline should be used as part of the treatment for chronic pain or fibromyalgia, however, only some patients achieve satisfactory pain relief [36].

• **Imipramine** was shown to be effective in the management of non-cancer pain, especially pain due to diabetes [26; 41].
• **Desipramine** relieves pain from postherpetic neuralgia, headache and diabetes [30].
• **Doxepin** relieved chronic pain [54].
• **Nortriptyline** was effective in diminishing chemotherapy-related pain [19] and orofacial pain [55].

It is also documented that TeCAs relieve chronic pain:

• **Amoxapine**, a second-generation antidepressant, was used in cancer pain management [39].
• **Maprotiline**, a second-generation antidepressant, relieved chronic pain, especially postherpetic neuralgia [57].

Selective serotonin reuptake inhibitors (SSRIs)

In the late 1980s, a new class of antidepressants with different chemical structures was introduced, the SSRIs, which are non-tricyclic drugs. They are characterized by causing inhibition of serotonin reuptake, but they do not block noradrenaline reuptake [3]. SSRIs are safe and commonly used, and their effect on relieving depression is well established. Potential side effects of SSRIs include decreased appetite and nausea, dry mouth, tremors, fatigue or drowsiness, increased heart rate and blood pressure and sexual problems. Nevertheless, they are thought to have fewer unpleasant side effects than the TCAs but are generally not as effective at treating chronic pain; however, they are used to treat certain types of headaches. The most common SSRIs used for chronic pain therapy are citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. Fluoxetine has been reported to block sodium channels, but the other SSRIs are not known to block sodium channels [9]. The SSRIs' pharmacological advantages result from the high selectivity for the serotonin receptor and the low or null affinity for other types of receptors, such as α-adrenergic, muscarinic, cholinergic and histaminic receptors [51]. Twenty trials available in the literature were analyzed by Smith et al. [49] to evaluate the efficacy of SSRIs in the treatment of chronic pain conditions; however, the results were conflicting.

SSRIs relieve chronic pain:

• **Citalopram**: two small trials (20 and 15 patients) indicated its small but significant analgesic effect on diabetes [48], but no effect was observed for fibromyalgia [38].
• **Fluoxetine**: one large trial (46 patients) revealed no apparent effect on diabetic nerve pain [30], but it did improve fibromyalgia pain [1].
• **Escitalopram** demonstrated efficacy and safety in the management of chronic low back pain [31].
• **Fluvoxamine** showed a lack of unequivocal evidence for pain relief of chronic pain.
• **Paroxetine**: two small trials (20 and 15 patients) indicated its weak analgesic effect on diabetes [48].
• **Sertraline** showed a lack of unequivocal evidence for the pain relief of chronic pain.

It seems that the older and the newer TCAs, which act as 'balanced' reuptake inhibitors, are more efficacious in terms of providing chronic pain relief than SSRIs.

Serotonin and norepinephrine reuptake inhibitors (SNRIs)

SNRIs cause a balanced inhibition of serotonin and noradrenaline reuptake [3]. SNRIs are newer antidepressants that are used to treat several types of chronic pain. They are thought to have fewer unpleasant side effects than TCAs, TeCAs and SSRIs, and they might be effective against chronic pain.

It is well documented that SNRIs relieve chronic pain:

• **Duloxetine** might help relieve both chronic pain and depression. Duloxetine is itself a potent balanced inhibitor of serotonin and noradrenaline reuptake, with no significant effect on a range of postsynaptic receptors or sodium channels [58]. Duloxetine demonstrated efficacy and safety in the management of chronic low back pain [31] but has some side effects (nausea, dry mouth and constipation). Current evidence strongly suggests that treatment with duloxetine may be beneficial in older adults with major depressive disorders and pain [10].
• **Venlafaxine** can raise blood pressure; therefore, overdose can be dangerous or fatal. Venlafaxine at low doses has a very similar action to SSRIs, as the serotonin reuptake inhibition predominates; however,

at high doses, noradrenaline reuptake inhibition is prominent. Venlafaxine has no postsynaptic effects, but it blocks sodium channels [24]. It was suggested that venlafaxine might work for some people resistant to other antidepressants. In 2009, treatment with venlafaxine was investigated in 186 patients with major depressive disorders whose treatments had failed with an SSRI or TCA. Moreover, 12 patients receiving venlafaxine for one year demonstrated improvement of chronic pain [29].

• **Desvenlafaxine** is a synthetic form of the major active metabolite of venlafaxine and causes similar effects.

• **Milnacipran** has equal affinity for the serotonin and noradrenaline reuptake sites, while duloxetine and venlafaxine have a 10- and 30-fold selectivity, respectively, for the serotonin reuptake site *versus* the noradrenaline reuptake site [50]. Milnacipran was examined in 125 patients with fibromyalgia and is now consider as a possible second-line drug treatment for fibromyalgia [17, 54].

Monoamine oxidase inhibitors (MAOIs)

MAOIs have no place in pain management, and little evidence from experimental studies exists for their analgesic effect [32]. In depression treatment, MAOIs are used as a last resort because of their numerous bothersome and potentially dangerous and serious side effects. The MAOIs that have no satisfactory effects on chronic pain, according to clinical data, are: harmaline, iproclozide, iproniazid, isocarboxazid, moclobemide nialamide, toloxatone and tranylcypromine.

Atypical antidepressants

These medications are called "atypical" because they do not fit into other categories, but they may also be effective at treating chronic pain, including dopamine-noradrenaline reuptake inhibitors and serotonin receptor modulators. Atypical antidepressants used for chronic pain treatment include:

• **Bupropion**, a second-generation non-tricyclic antidepressant that is a noradrenaline and dopamine reuptake inhibitor without the postsynaptic effects [3]. A study of patients with various forms of chronic pain has shown that bupropion is effective [44]. Bupropion has several clinical contraindications, such as seizure, eating disorder, activating effect for some patients and a few sexual side effects. Bupropion might also suppress appetite, and it might help with smoking cessation.

• **Trazodone** is a serotonin antagonist and reuptake inhibitor, and it has anti-anxiety (anxiolytic) and sleep-inducing (hypnotic) effects. Trazodone has considerably fewer prominent anticholinergic (dry mouth, constipation and tachycardia) and sexual side effects, but the clinical trials did not confer its beneficial effects for chronic pain.

• **Mirtazapine** has a unique pharmacological profile; it increases 5-HT_{1A}-mediated neurotransmission, has a strong antagonism for α_2 adrenergic and 5-HT_2 and 5-HT_3 serotoninergic receptors and a minimum effect on amine reuptake [8]. Mirtazapine can be used as an optional treatment for headaches and nausea [28] and for resolving insomnia, anxiety and depressive symptoms in cancer pain patients [7].

• **Nefazodone** antagonizes the action of 5-HT_2 receptors and inhibits noradrenaline and serotonin reuptake. The 5-HT_2-receptor antagonism increases 5-HT_{1A} receptor binding [12]. Thus, the mechanism of action is believed to be due to a net effect of increased neurotransmission. Nefazodone has the double advantage of a weak affinity for α_1- and β-adrenergic receptors and no activity with histaminic, dopaminergic or muscarinic cholinergic receptors, resulting in a signifi-

Tab. 2. Antidepressants used in neuropathic pain treatment

Groups	Drugs	References
TCA	Amitriptyline Doxepin Imipramine Nortriptyline	[36] [54] [41] [19]
TeCA	Amoxapine Maprotiline	[39] [57]
SSRI	Citalopram Fluoxetine Paroxetine	[48] [1, 30] [48]
SNRI	Duloxetine Venlafaxine Milnacipran	[10, 31] [11] [17, 54]
MAOI	–	–
Atypical antidepressant	Bupropion	[45]

cantly lower incidence of side effects. However, nefazodone has been linked to dangerous liver problems. There are no published reports on nefazodone in pain management, but experimental studies suggest its analgesic properties [40].

Usefulness of antidepressants for attenuating neuropathic pain (Tab. 2)

Antidepressants in the treatment of neuropathic pain

Neuropathic pain is difficult to treat, however, several treatment options with reasonable efficacy are available at the present time. Opioids and NSAIDs are only partially effective, therefore, there is a need to use adjuvant analgesics. Neuropathic pain affects 6–8% of the general population, and its impact on quality of life, mood and sleep exceeds the burden of its causative pathology [48]. The characteristic syndromes of neuropathic pain (allodynia and hyperalgesia) develop as a result of damage to nerves in consequence of tumors, multiple sclerosis, diabetes, herpes zoster, AIDS and many neurological diseases, such as peripheral neuropathy, radiculopathy, spinal cord injury and stroke [42, 48]. Antidepressants were used in painful diabetic neuropathy based on empirical observations in 1977 by Davis and co-workers, but their potential analgesic properties were noted shortly after their use. Clinical studies have shown that TCAs tend to work better than an anticonvulsant (gabapentin) and opioid (tramadol and oxycodone) drugs, whereas venlafaxine from the SNRI group appears to be equally effective, and SSRIs appear to have lower efficacy [11, 46, 48]. Ryder and Stannard [43] have shown that, from 100 patients with prescribed antidepressants for neuropathic pain, 30 patients will obtain 50% pain relief, 30 patients will have minor adverse reactions and 4 patients will stop treatment because of major adverse effects. Beneficial effects on sleep usually appear within a few days of treatment, whereas the improvement in pain will take a week or longer [43]. Table 1 shows the antidepressants suitable for use in the treatment of neuropathic pain. The exact mechanism of the analgesic action of antidepressants is not yet clear; however, it is well established that repeatedly administered antidepressants work in patients with both normal and depressed moods in a number of neuropathic pain conditions [27, 30].

The painkilling mechanism of these drugs under neuropathic pain conditions is still a matter of study. These studies have shown that doses necessary to attenuate pain are often lower than those used to treat depression, and the onset of activity is more rapid at these doses. Additionally, these studies have shown that analgesic efficacy is usually obtained in non-depressed patients and does not correlate with improvement in mood in depressed patients, and the drugs are useful in acute and experimental pain. Ryder and Stannard [43] have published that almost 50% of patients with pain have depression, but antidepressants are prescribed in the pain clinic for their specific analgesic effects rather than their mood altering effects; however, the latter is also very important in chronic pain patients. Antidepressants might increase neurotransmitters in the spinal cord that reduce pain signals, but it takes time to experience pain relief (sometimes up to one or more weeks). Jain and Jain [22] have stressed that neuropathic pain and depression have a shared neurobiology and appear to have a shared neuroanatomy (in the brain and spinal cord) and neurochemistry (noradrenaline and serotonin), with similar hypothalamic-pituitary-adrenal axis, autonomic nervous system and inflammatory cytokine disturbances [22].

TCAs remain one of the first-line therapies for neuropathic pain, such as postherpetic neuralgia (amitriptyline, nortriptyline, and desipramine) and painful diabetic neuropathy (triptyline, desipramine, clomipramine, imipramine, and nortriptyline) [32]. Comparative studies show that TCAs (amitriptyline, doxepin, imipramine) with balanced noradrenergic and serotonergic effects are more effective than TeCAs (maprotiline) with anticholinergic properties and selective serotonin reuptake inhibitors from the SSRI group (citalopram, fluoxetine, paroxetine) [43, 47]. TCAs might relieve neuropathic pain by their unique ability to block monoamine uptake in the CNS, specifically serotonin and/or noradrenaline, in addition to other neurotransmitters. They might alter nociceptive processing by prolonging synaptic activity of these monoamines, thereby enhancing descending inhibitory action in the spinal cord and having monoaminergic effects elsewhere in the CNS [23]. To a varying degree, the antidepressants also block a number of other receptor types involved in pain processing, including α-adrenergic, H_1-histaminergic and *N*-

methyl-D-aspartate (NMDA) receptors. They also block the effects on calcium and sodium channels and are weak stimulators of μ-opioid receptors. A recent study suggests that antidepressant treatment appears to positively impact immune/cytokine deregulation [22]. Research data indicate that antidepressants can reduce levels of inflammatory cytokines, such as tumor necrosis factor α and interleukin-6 [5]. The hyperexcitability of NMDA receptors is one of the factors in the genesis of neuropathic pain. Ketamine (an NMDA receptor antagonist) is useful for treating neuropathic pain. Some studies show that TCAs are NMDA receptor-like antagonists, although this effect might not be fully present when the drug is used in therapeutic concentrations. Neuronal spontaneous activity, caused by sodium and calcium channels, leads to neuropathic pain; therefore, the unspecific sodium channel blocker lidocaine relieves central pain [2], and the anticonvulsant drug gabapentin clearly relieves neuropathic pain. The TCAs also potently inhibit sodium and L-type calcium channels and therefore act as sodium and calcium channel blockers, respectively, in neuropathic pain [14]. In summary, the effectiveness of TCAs in neuropathic pain is most likely multimodal, with contribution of monoamine reuptake inhibition and blockade of NMDA receptors, sodium channels and calcium channels.

Several clinical studies have shown that the SSRI-like drugs citalopram, fluoxetine and paroxetine can be effective in painful diabetic neuropathy [1, 30, 48]; however, the drugs from this group are generally less effective for neuropathy than TCAs, TeCAs and SNRI.

A number of positive trials have been published on the SNRIs group, including the use of duloxetine, venlafaxine, and milnacipran for neuropathic pain [54]. In the model of neuropathic pain, venlafaxine and duloxetine both have a significant antinociceptive effect [32]. In addition, our results [in preparation] suggest that not only venlafaxine and duloxetine but also milnacipran have similar antinociceptive effects in both rat and mouse neuropathic pain models. Venlafaxine and duloxetine should be second-choice treatments in painful diabetic neuropathy [54]. In the elderly and in patients with cardiovascular risk factors, it is suggested that SNRIs should be preferred over TCAs. Venlafaxine is the most investigated of these new drugs in neuropathic pain management. Many cases reports have shown that venlafaxine is effective for relieving pain in different types of peripheral neuropathies, such as postherpetic neuralgia, intercostal neuralgia, peripheral diabetic neuropathy and atypical facial pain. The use of venlafaxine is recommended as a second choice after other therapies (e.g., NSAIDs and other antidepressants) because of either their inefficacy or the intolerable presence of side effects. In the treatment of post-herpetic neuralgia, venlafaxine was effective, especially when associated with GABAergic drugs (e.g., gabapentin) due to a possible synergy between the two drugs [29].

The MAOI antidepressants are not used to treat neuropathic pain in the clinic [32]. From the atypical antidepressant group, bupropion provided substantial neuropathic pain relief in a study by Semenchuck et al. [44]. The results from this study suggest the possibility that a dopaminergic effect could enhance the peripheral neuropathic pain-relieving effect obtained with serotonergic and noradrenergic mechanisms [32].

Combination of antidepressants with other treatments

The effect of combining antidepressants with other drugs in neuropathic pain needs additional research. Combining venlafaxine with gabapentin, if the latter provided insufficient pain relief in painful diabetic neuropathy, resulted in a significant additional effect [46]. Thus, TCAs and venlafaxine could be combined with gabapentin and with opioids, with the exception of tramadol because it interferes with the monoaminergic system and has an opioid effect, therefore, combination of different antidepressant classes should be avoided with this drug. Clinical studies on the use of nefazodone in pain treatment are not yet available. In an experimental study on rats, nefazodone was shown to have analgesic properties, especially when associated with morphine. In fact, nefazodone seems to be able to increase the analgesic effect on the μ-opioid receptor, without effecting lethality or gastroenteric motility [29]. It is also very important to remember that antidepressants administered together with other drugs can participate in pharmacodynamic interactions. Some drugs can add their own contribution to antidepressant-related risks of serotonin syndrome (e.g., antimigraine agents, cocaine, amphetamines or ecstasy and antibiotics, such as linezolid), seizure induction (e.g., antipsychotics, stimulants, alcohol, fluoroquinolone antibiotics, such as isoniazid, and antiasthmatics), ventricular arrhythmias (e.g., antiarrhythmic agents, antiepileptics, antipsychotics, methadone, and macrolide antibiotics) or gastrointestinal

bleeding (e.g., anti-inflammatory agents and anticoagulants). In conclusion, antidepressants in the TCA and SNRI groups are fairly effective in peripheral neuropathic pain, whereas SSRIs have a low efficacy.

Analgesics acting by both opioid receptors and aminergic reuptake inhibitors

Neuropathic pain is generally considered to be difficult to treat because of low affectivity of μ-opioid receptor agonists. Activation of the opioid receptors and norepinephrine and/or serotonin reuptake inhibition is currently suggested as an analgesic treatment in neuropathic pain.

Tramadol is an atypical, racemic opioid that combines weak μ-opioid receptor activation with inhibition of norepinephrine and serotonin reuptake (the mechanisms common to antidepressants). Tramadol also acts as an NMDA receptor antagonist, 5-HT_{2C} receptor antagonist, (α7)5 nicotinic acetylcholine receptor antagonist, $TRPV_1$ receptor agonist, and an M_1 and M_3 muscarinic acetylcholine receptor antagonist. This combination of complementary mechanisms of action results in potent analgesic activity in neuropathic pain. The contribution of non-opioid activity is demonstrated by the fact that the analgesic effect of tramadol is not fully antagonized by the μ-opioid receptor antagonist – naloxone. Tramadol is metabolized to O-desmethyltramadol, a significantly more potent μ-opioid agonist. Tramadol and its major metabolite are distinguished from other more potent opioid agonists by their relative selectivity for μ-opioid receptors.

Tapentadol (3-[(1R, 2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol) is a centrally acting analgesic of a new substance class for the treatment of severe nociceptive and neuropathic pain. Tapentadol combines μ-opioid receptor agonism and selective norepinephrine reuptake inhibition into one molecule. Because of its combined mechanisms of action, tapentadol offers a broad therapeutic spectrum for nociceptive and neuropathic pain. In different animal models, its high efficacy was shown in acute nociceptive, acute and chronic inflammatory as well as chronic neuropathic pain. Using several preclinical approaches, it was shown that the noradrenergic component of tapentadol interacts with the opioid component and that both synergistically contribute to the high analgesic effect of the substance. In comparison to known drugs with only one of the two modes of action, tapentadol has an improved tolerability profile in the relevant animal models, particularly with regard to gastrointestinal and central side effects, despite its high potency [53].

Experiments on animal model of neuropathic pain

Experimental findings demonstrated that the antidepressants used have an antinociceptive effect on rat and mice neuropathic pain conditions [60–63]. The analgesic effects of TCAs, such as amitriptyline, have been examined using a variety of animal models of pain, and they have been shown to have antinociceptive and antiallodynic effects when administered systemically, spinally, supraspinally and locally [6]. We, as well as others, have shown that subcutaneously, intraperitoneal and intrathecal administration of milnacipran and venlafaxine (SNRIs), fluoxetine (an SSRI), and amitriptyline and doxepin (TCAs) reduce pain syndromes in a rat model of neuropathic pain [43, 48, 59]. Milnacipran is thus similar to the TCAs, which also inhibit the reuptake of both serotonin and noradrenaline. A major difference, however, between the actions of milnacipran and the TCAs is that the former compound is devoid of interactions at neurotransmitter receptors and is thus devoid of the troublesome adverse effects that these interactions cause. In rats, milnacipran has been reported to have antiallodynic and antihyperalgesic effects on neuropathic pain. These effects are similar to duloxetine, which has been shown to significantly attenuate inflammatory and diabetic pain by intraperitoneal, intrathecal, and intracisternal administration. Korzeniewska-Rybicka and Płaźnik [25] examined the influence of imipramine, amitriptyline, citalopram and maprotiline on the nociceptive response. Their results indicate that there is a disparate sensitivity to antidepressant treatment of differently evoked behavioral reactions to the nociceptive stimuli. They also showed that the most potent effects of administered antidepressants are in the model of visceral pain, and there is no relationship between the analgesic and antidepressant-like effects of the antidepressants compounds that they examined.

In the rat model of neuropathic pain, animals developed hyperalgesia and allodynia in parallel with microglial activation [35, 56]. Our results of western blot analysis [in preparation] are interesting because antidepressants, such as milnacipran, venlafaxine,

fluoxetine, amitriptyline and doxepin, reduce similar pain syndromes; however, these drugs demonstrate a different influence on microglial activation under neuropathic pain conditions. In the lumbar part of the spinal cord, we observed that microglial changes are enhanced in neuropathic pain after single administration of amitriptyline, doxepin and milnacipran, and the opposite effect was observed for venlafaxine and fluoxetine. Simultaneously, we did not observe changes in astroglial cell activation. Therefore, we verified the influence of chronic administration of minocycline (microglial inhibitor) on the effectiveness of selected antidepressants. The results showed that a single administration of fluoxetine, milnacipran and amitriptyline after chronic administration of minocycline increased its effectiveness, measured by von Frey and cold plate tests. This result might suggest involvement of microglial cells in the effectiveness of these drugs. The results are interesting and need to be studied further.

Summary

In summary, more preclinical and controlled clinical trials might establish the safety and efficacy of antidepressant use in neuropathic pain. There is an experimental basis for the use of antidepressants in chronic pain, but there is still a need for future preclinical behavioral and biochemical studies due to their different mechanism of action.

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