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Antidepressants and pain

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Tricyclic antidepressants, together with anticonvulsants, are considered to be first-line drugs for the treatment of neuropathic pain. Antidepressants are analgesic in patients with chronic pain and no concomitant depression, indicating that the analgesic and antidepressant effects occur independently. The analgesia induced by these drugs seems to be centrally mediated but consistent evidence also indicates a peripheral site of action. Several pharmacological mechanisms account for their antinociceptive effect but the inhibition of monoamine transporters (and, consequently, the facilitation of descending inhibition pain systems) is implicated on the basis of mechanistic and knockout-mouse studies. However, pain is a common symptom of depression, and depression is frequent in chronic pain patients, supporting the hypothesis that pain and depression share some common biochemical mechanisms. We suggest that antidepressants have a genuine analgesic effect and that research into their mechanisms of action will help to facilitate the development of new drugs.

Why use an antidepressant to relieve pain?*

'Why do I have to take an antidepressant to relieve pain if I am not depressed?' This question could be asked of a physician by a patient suffering from pain when prescribed an antidepressant as an analgesic. This is a reasonable question from the patient's perspective, and the physician should answer that the antidepressant is prescribed for its analgesic action rather than its antidepressant action. The patient's next questions might be: 'are antidepressants pain killers?' and 'how is that possible?'

Many drugs are currently used to treat pain. All of them can modulate the known peripheral and central systems that are implicated in the detection, transmission, modulation and integration of nociceptive processes, providing an effective analgesic effect in different painful situations. Among these drugs, antidepressants are perhaps the least well-known in terms of analgesic mechanism of action, despite their extensive use in pain treatment.

According to a recent survey carried out in 15 European countries, antidepressants represent 3% of all the analgesic prescriptions currently used to treat chronic pain, the same percentage as for triptans [1]. By contrast, weak and strong opioids represent 28%, and paracetamol and nonsteroidal anti-inflammatory drugs 62%. In a large observational European cross-sectional survey centred in neuropathic pain, 29% of patients were prescribed antidepressant drugs [2].

For a long time, antidepressants were not considered to be analgesic drugs but, because of their action on neuronal circuits that regulate emotion (an essential component of pain), they were considered to achieve an integral alleviation of pain. In other words, antidepressants were not thought to be analgesic, only antidepressant. However, although they can act as antidepressants in some circumstances and in certain patients with chronic pain, they have a genuine analgesic action that has been demonstrated in both experimental and clinical conditions [3]. The analgesic efficacy of antidepressants in patients with chronic pain and no concomitant depression, or the demonstration of analgesic effect without any effect on mood in depressed chronic-pain patients attests to this [4]. Further supporting the credibility of the intrinsic analgesic action of antidepressants, the dose required to achieve an optimum analgesic response is usually lower than that required to achieve an antidepressant effect [5]. The variation in analgesic efficacy among chemical classes of antidepressant is further proof of the analgesic response being distinct from effects on mood. Moreover, the delay of action of antidepressants in chronic pain management in some studies is shorter than in depression [5,6]. Furthermore, in some cases, it cannot be excluded that the degree or nature of mood dysfunction in chronic pain patients is not the same as in patients in which depression is the primary disorder. If this were the case, it might be argued speculatively that alleviation of the underlying pain symptoms by antidepressants might be associated with subsequent improvement of depressive symptoms, despite the antidepressants being used at lower doses. That is, improvement in pain would lead to improvement in mood. The neurobiological reasons for this are unclear but it is supposed that, given that pain induces emotional and

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* Pain syndromes can be distinguished by either: (i) duration – they can be classified as acute pain of short duration (e.g. postoperative pain) or chronic pain prolonged for several (at least six) months (e.g. cancer pain); or (ii) aetiological mechanism – the two main classes of which are 'nociceptive pain', which is caused by tissue injury, with an inflammatory reaction that can happen on various, superficial (i.e. skin, muscle or joint) or deep (viscera), tissues and 'neuropathic pain' (pain initiated or caused by a primary lesion or dysfunction of the nervous system), which is caused by diabetes, HIV, zoster, trauma, various drugs (e.g. anticancer drugs) or injury of the CNS. Sine materia pain has also been identified (e.g. fibromyalgia). Non-cancer pain is also called benign or non-malignant pain.

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sensory mechanisms, the stabilization of one influences the other to some degree.

Although antidepressants have been used as analgesic drugs for ~40 years, they have only recently been approved by drug regulatory agencies for specific use in neuropathic pain, specifically diabetic neuropathy [7]. In the meantime, antidepressants have appeared in virtually all therapeutic guidelines for the treatment of chronic pain, both so-called benign pain (e.g. neuropathy and headache) and cancer pain (see http://www.theacpa.org). This recognition as analgesics has been made possible by a large number of studies published as case reports, open-label studies or controlled clinical trials for which their efficacy has been reported [8]. However, such studies are difficult to compare, which has significantly delayed the establishment of antidepressants as analgesics. The main differences among the studies relate to the type of pain treated, the type of antidepressant chosen, the recommended doses or the duration of treatment. A further problem is that some studies did not use adequate scales to measure the potential associated depression. However, some published meta-analyses have assessed all of these circumstances and concluded that antidepressants are useful drugs for chronic pain management, especially neuropathic pain [9].

Tricyclic antidepressants versus selective amine-reuptake inhibitors and new dual antidepressants

Just as there is virtually an agreement that neuropathic pain is most responsive to the analgesic action of antidepressants [10], a consensus also exists that the well-known tricyclic antidepressants have the greatest analgesic efficacy [8,9] (Table 1). Among these, particular mention should go to amitriptyline, the gold standard of analgesic antidepressants. This does not mean that other tricyclic antidepressants are less effective but that most available clinical evidence has been obtained for amitriptyline [11]. When tricyclic antidepressants are used as analgesic drugs, their undesirable effects occur less commonly and are less severe than when they are used as antidepressants, mainly because much lower doses are used in the former.

Based on safety – rather than efficacy – criteria, selective 5-HT-reuptake inhibitor (SSRI) antidepressants have been used to treat chronic pain. In this respect, there are some clinical studies showing the efficacy of fluoxetine, citalopram, fluvoxamine, sertraline and paroxetine. However, the analgesia obtained is less consistent than that brought about by tricyclic antidepressants [2,9] (Table 1), although the reason for this limited efficacy is not understood and would be interesting to study. New non-tricyclic selective noradrenaline-reuptake inhibitors such as reboxetine have been less widely used as analgesics [12]. Other non-tricyclic antidepressants that inhibit noradrenaline and 5-HT reuptake but have no action on the muscarinic acetylcholine receptors, histamine receptors or α-adrenoceptors responsible for the side-effects of tricyclics have recently appeared, and controlled trials are needed to elucidate their role in the treatment of chronic pain. Such antidepressants include venlafaxine, milnacipran and duloxetine, for which several clinical studies have been conducted in various forms of chronic pain, with positive results being obtained [13]; in some studies, however, venlafaxine and minalcipran were modestly effective or failed to show a better efficacy than placebo. In the clinical studies reported to date, non-tricyclic antidepressants have shown a better tolerability than have tricyclics. Duloxetine was the first antidepressant to be approved by the Food and Drug Administration [FDA (http://www.fda.gov/)] for treating neuropathic pain in diabetic patients [7]. Other antidepressants that are not specific noradrenaline- or 5-HT-reuptake inhibitors, such as trazodone, mirtazapine, mianserine and nefazodone, have also shown an analgesic action in some cases [14]. There is a lack of evidence regarding the effectiveness of monoamine oxidase (MAO) inhibitors such as moclobemide. Bupropion, a dopamine-reuptake inhibitor that also inhibits noradrenaline reuptake, has shown some efficacy in cases of neuropathic pain treatment [15].

Tricyclic and, perhaps, new dual antidepressants are the most effective drugs of this group for neuropathic pain management [13]. However, one must keep in mind that the efficacy of these drugs (as for anticonvulsants – other drugs used in this context) is limited, as assessed by meta-analyses; the number needed to treat [the number of patients treated to improve the health of one patient (at least 50% decrease in pain intensity)] ranges from 2.7 to 3.7 for tricyclics in neuropathic pain [9].

Mechanism of the analgesic action of antidepressants

Most information regarding the mechanism of the analgesic action of antidepressants has been obtained in

Table 1. Analgesic efficacy of antidepressants

Antidepressant	Animals[a]			Humans[b]	
	Number of studies	Positive results		Number of studies	Combined NNT[c]
TCAs	126	Acute pain tests	81%	23	3.1
		Chronic pain models	95%		
SSRIs[d]	39	Acute pain tests	44%	3	6.8
		Chronic pain models	33%		
SNRIs[e]	10	Acute pain tests	100%	3	5.5
		Chronic pain models	100%		
Others[f]	7	Acute pain tests	100%	1	1.6 (bupropion: only one study)
		Chronic pain models	100%		

[a]Data adapted from Ref. [31] and complete up to 2005. Only ~10% of the animal studies were performed using chronic pain models.
[b]Data from Ref. [9].
[c]Number of patients treated to improve the health of one patient (at least 50% decrease in pain intensity).
[d]For example, fluoxetine, fluvoxamine, sertraline, paroxetine and citalopram.
[e]For example, venlafaxine, minalcipran, duloxetine.
[f]For example, mirtazapine, bupropion.

animals (rats and mice). It should be noted that the results of research into the antinociceptive action of antidepressants using acute pain tests in which different noxious stimuli (thermal, chemical, mechanical or electric) are applied cannot be extrapolated to human clinical pain [16]. In fact, antidepressants are never used to treat acute pain in humans, except for experimental research. Moreover, this approach seems to be inadequate for several other reasons: (i) acute administrations are often used, whereas antidepressants are used as a long-term treatment; (ii) acute pain tests do not involve the neuroplastic changes that are observed during chronic pain; and (iii) the affective component of pain cannot be detected in such models. Fortunately, there has recently been a significant trend towards using different chronic pain models, mainly neuropathic ones (e.g. chronic constriction injury, partial sciatic nerve ligation, L5 or L5–L6 spinal nerve ligation, selective spinal nerve ligation, streptozocin-induced diabetic neuropathy and chemotherapy-induced neuropathy), that mimic clinical situations more closely, thus providing much more valuable information [16]. However, it is difficult to dissociate the sensory and affective components of pain processing in rodents, and an understanding of the underlying mechanisms of each component is unclear. Recently, a behavioural test paradigm has been developed that measures the aversiveness of nociceptive stimuli in an attempt to model the affective or motivational aspect of clinical pain states [17]. If generalized, this method would be of great interest for exploring the effect of antidepressants on the sensory and affective components of pain. An effort is needed from the community of pain researchers to explore these two aspects – including the assessment of refined behaviour rather than just reflex nociceptive responses, and the use of chronic pain models and repeated administrations of antidepressants.

Furthermore, some studies in which the analgesic action of antidepressants has been investigated in different knockout mice have provided excellent information (Box 1). Many believe that the increased availability of noradrenaline and 5-HT in the synaptic cleft is the main, but not the only possible, mechanism of the analgesic action of antidepressants (Table 2). Such action would result from inhibition of the reuptake of these two monoamines (and dopamine) by blockade of their specific transporters in the presynaptic membrane. Noradrenaline and 5-HT, and their receptors, are greatly involved in regulating nociceptive sensation at different levels of the nervous system. In this regard, antidepressants seem to enhance endogenous pain control and are considered to increase or maintain the activity of the descending inhibitory bulbospinal pathway, which is compromised in chronic pain conditions [18] (Figure 1). This effect can be increased by blocking 5-HT_{1A} receptors (which have a pronociceptive influence), as shown for antidepressant activity [19–21]. Antidepressants have significant pharmacological actions at crucial areas and nuclei involved in this circuit, such as the locus coeruleus nucleus, the dorsal and magnus nuclei in the raphe and the dorsal horn of the spinal cord. Thus, antidepressants can facilitate the endogenous pain control system acting at this neuroanatomical level [22], resulting in an increase in nociceptive threshold.

Most studies of antidepressants have focused on their central analgesic action (supraspinal or spinal). However, a peripheral analgesic mechanism of action has also been suggested [23] (Figure 1). This notion is based on the effects obtained with some antidepressants in various animal models with an inflammatory component, such as the formalin test, carrageenin and chronic arthritis models induced by Freund's adjuvant, and other models such as visceral pain. At the peripheral site, it is unlikely that the analgesic mechanism of action is an increased availability of noradrenaline or 5-HT because both of these monoamines enhance nociceptive transmission at this level. The analgesic mechanism of action at this level is probably the blockade of noradrenoceptors, 5-HT receptors, histamine receptors or muscarinic acetylcholine receptors. Interestingly, adenosine also seems to contribute to peripheral analgesia [23]. It has been reported that antidepressants enhance adenosine transmission, increasing extracellular adenosine levels. Thus, the peripheral analgesic effect of amitriptyline is blocked by adenosine receptor antagonists [24,25].

Overall, tricyclic antidepressants could be more effective than other selective antidepressants at treating pain because they act on multiple nociceptive targets at central and peripheral levels (Table 2).

Box 1. Antidepressants and pain: lessons from knockout mice

Mice deficient in 5-HT or the NE transporter (5-$HTT^{-/-}$ mice and $NET^{-/-}$ mice, respectively) are regarded as models of lifelong treatment with serotonin- or noradrenaline-reuptake inhibitors [69,70]. In fact, these knockout mice resemble mice treated with antidepressants in several tests that are classically used to assess the actions of antidepressants. Moreover, these mice show alterations in pain sensitivity, and data collected from them could provide interesting information for understanding the analgesic effects of antidepressants. For example, 5-$HTT^{-/-}$ mice do not develop thermal hyperalgesia, but show bilateral mechanical allodynia after nerve injury, which has been explained in terms of a lack of 5-HT spinal inhibition [71]; interestingly, tricyclic antidepressants produce a consistent antinociceptive effect on heat hyperalgesia but not on mechanical and cold allodynia. Recently, the analgesic efficacy of fluoxetine, amitriptyline and duloxetine has been evaluated in a special type of knockout mouse: the Lmx1b conditional knockout (Lmx1b CKO) mouse. The transcription factor Lmx1b is essential for the development of 5-HT-containing neurons. Lmx1b CKO mice lack all 5-HT markers in the brain and spinal cord. The antinociceptive effects of these antidepressants are reduced in Lmx1b CKO mice, indicating that 5-HT is essential in the analgesia induced by different classes of antidepressant [72]. By contrast, morphine analgesia is increased in $NET^{-/-}$ mice [73], which is consistent with the way tricyclic antidepressants enhance opiate analgesia in normal animals [48]. The enhancement of morphine analgesia in $NET^{-/-}$ mice is attributed to the activation of α_2-adrenoceptors; interestingly, the analgesic effect of amitriptyline is reduced in α_2-adrenoceptor-knockout mice [37].

Table 2. Proposed mechanisms of action of the analgesic effect of antidepressants[a]

Pain mechanisms	Comments	Antidepressant	Refs
5-HT mediated	↑ 5-HT availability		
	Blockade of neural reuptake	TCAs, SNRIs, SSRIs	[b]
	Inhibition of MAO	IMAOs	[b]
	5-HT_{1A} receptors	SNRI: venlafaxine	[32]
		Atypical: trazodone	[33]
	5-HT_2 receptors	TCAs: imipramine, nortriptyline, maprotiline	[34]
		SNRIs: milnacipran	[34]
		SSRIs: fluoxetine, fluvoxamine	[20,34]
		NRIs: nisoxetine	[34]
	5-HT_3 receptors	TCAs: imipramine	[34]
		Atypical: trazodone	[33]
Noradrenaline mechanism	↑ Noradrenaline availability		
	Blockade of neural reuptake	NRIs, TCAs, SNRIs	[b]
	Inhibition of MAO	IMAOs	[b]
	α_2-Adrenoceptors	TCAs: amitriptyline, imipramine, dothiepin	[35–37]
		SNRIs: milnacipran, venlafaxine	[38,39]
		NRIs: reboxetine, (+)-oxaprotiline, (−)-oxaprotiline	[36,40]
		SSRI: paroxetine	[36]
		Atypical: mirtazapine	[38]
		IMAO: moclobemide	[41]
	α_1-Adrenoceptors	TCAs: imipramine, nortriptyline, maprotiline	[34]
		SNRI: milnacipran	[34]
		NRI: nisoxetine	[34]
	β_1- and β_2-adrenoceptors	TCAs: desipramine, nortriptyline	[42]
Dopamine mediated	↑ Dopamine availability		
	Blockade of neural reuptake	DNRIs	[b]
	D_2 receptor activation	DNRI: nomifensine	[43]
Opioid mediated	Activation of opioid endogenous system: δ-opioid receptors (supraspinal level) and μ-opioid receptors (spinal level)	TCAs: amitriptyline, clomipramine, desmethylclomipramine, imipramine, desipramine, maprotiline, nortriptyline, amoxapine, dothiepin	[44–49]
		SNRI: venlafaxine	[50]
		SSRI: paroxetine	[44]
		NRIs: (+)-oxaprotiline, viloxazine	[44,49]
		DNRI: nomifensine	[49]
		Atypical: nefazodone, mirtazapine, mianserin	[38,49,51]
Ion channels			
Na^+ channels	Blockade	TCAs: amitriptyline, imipramine, trimipramine, desipramine, doxepin	[52]
K^+ channels	Activation	TCAs: amitriptyline, clomipramine	[53]
Ca^{2+} channels	Inverse correlation between increase in Ca^{2+} channel density and analgesic effect; Ca^{2+}-uptake inhibition	TCAs: amitriptyline, clomipramine, imipramine, trimipramine, desipramine, doxepin	[53–56]
		SSRI: citalopram	[54]
		NRI: oxaprotiline	[56]
Adenosine	↑ Adenosine availability; local release of adenosine; activation of adenosine A_1 receptor	TCA: amitriptyline	[24,25,57]
NMDA receptors	Central level: inhibits NMDA-induced spinal hyperalgesia	TCAs: amitriptyline, desipramine	[58,59]
	Peripheral level: Potentiated by NMDA receptor antagonists	TCAs: clomipramine, desipramine	[47]
$GABA_B$ receptors	↑ $GABA_B$ receptor function	TCAs: amitriptyline, desipramine	[60–62]
		SSRI: fluoxetine	
Substance P	↓ Substance-P-induced behaviour; ↓ production of substance P	TCAs: imipramine, clomipramine	[63,64]
		SSRI: fluoxetine	[63]
P2X receptors	Peripheral modulation	TCA: amitriptyline	[65]
Inflammatory and immune parameters	↓ Prostaglandin-E2-like activity	TCAs: amitriptyline, clomipramine	[63,66]
		SSRI: fluoxetine	[66]
	↓ NO release	TCA: amitriptyline	[66]
		SSRI: fluoxetine	[66]
	↓ Migration of macrophages	TCA: clomipramine	[67]
	↓ Production of TNF-α	TCA: amitriptyline	[68]

[a]Abbreviations: DNRI, dopamine-, noradrenaline-reuptake inhibitors; IMAO, monoamine oxidase inhibitor; NO, nitric oxide; NRI, noradrenaline-reuptake inhibitor; SNRI, 5-HT-, noradrenaline-reuptake inhibitor; TCA, tricyclic antidepressant; TNF-α, tumour necrosis factor α.
[b]See main text.

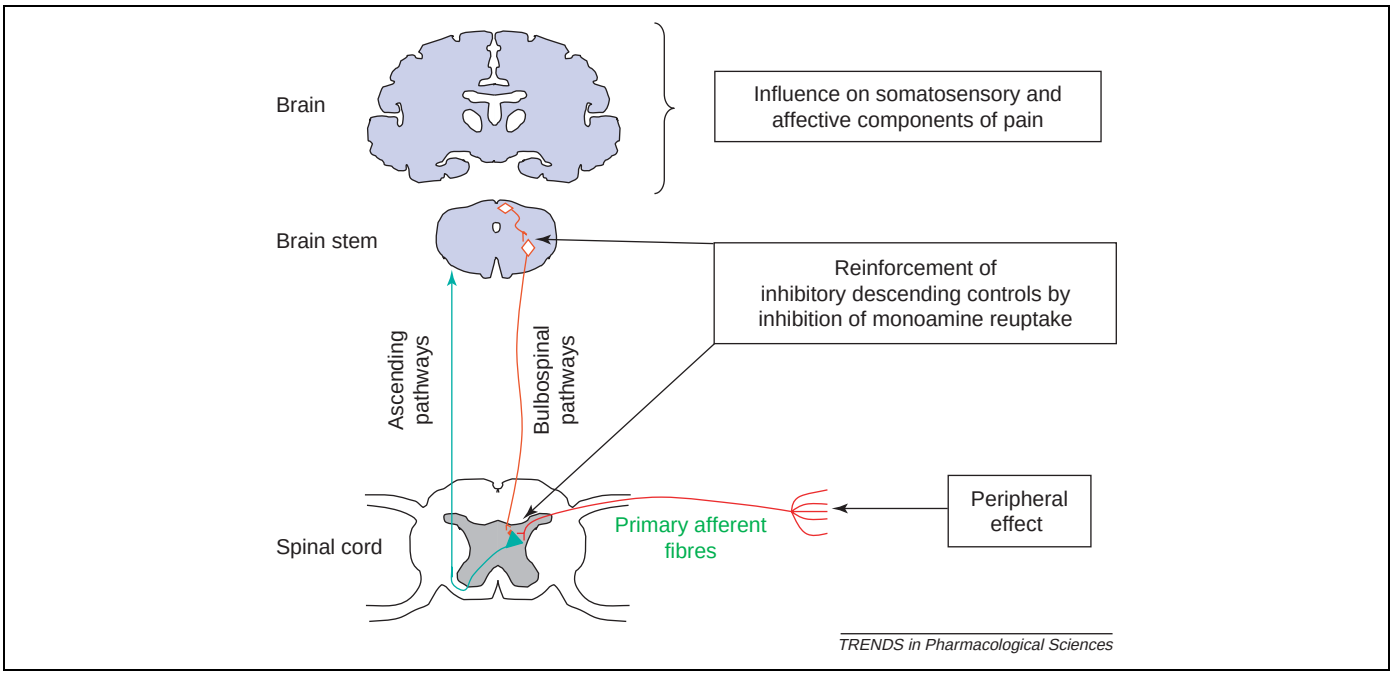

Figure 1. Postulated sites of the analgesic action of antidepressants. The analgesic effect of antidepressants is thought to be centrally mediated. The classical mechanism is the reinforcement of monoamine-containing bulbospinal pathways by either acting on the terminals of these fibres at the spinal level or reinforcing these pathways at the brain stem level. A supraspinal effect in the brain might be involved, although further studies are needed to demonstrate this. Finally, some studies have demonstrated a peripheral action of antidepressants, which might be of primary relevance to localized delivery methods (e.g. topical application), but its involvement in the effect of systemically administered antidepressants has not been demonstrated.

Impact of antidepressants on pain as a physical symptom of depression

Pain and depression are often linked, and several studies have indicated that pain and depression share common neurochemical mechanisms [26,27]. Clinical depression is common in patients with persistent chronic pain: 30–54% [28]. Conversely, pain is among the most common physical symptoms in patients with depression, and a common complaint reported to specialists [29]. Relapses into a depressive state are more common in such patients and make total symptom remission difficult, closing a vicious cycle: depression–pain–depression. It has been suggested that the use of an antidepressant with analgesic action would help these patients, preventing relapse and enabling the achievement of total symptom remission [30]. However, long-term clinical studies are required to ascertain this. Moreover, such clinical studies should be designed to assess specifically whether remission is actually achieved as a result of pain improvement. In any case, when antidepressants are used to achieve an integral improvement in depressive condition that includes pain as a symptom or to improve the affective emotional condition associated with chronic pain, antidepressant doses must be used to improve both symptoms.

Whether antidepressants can improve the affective component of pain, in addition to alleviating its somatosensory component, is a controversial subject and a challenge in clinical research. Pain has several components; as stated in the International Association for the Study of Pain (http://www.iasp-pain.org/) definition, pain is 'an unpleasant sensory and emotional experience'. Based on the studies conducted to date, it cannot be affirmed that antidepressants are analgesics because they improve the emotional response to pain and have an impact on the somatosensory component. However, some areas of the CNS that integrate the emotional and affective components of pain, such as the anterior cingulate cortex and amygdala, are susceptible to regulation by antidepressants in both pain conditions and depression.

Concluding remarks and future perspectives

Antidepressants have become, in their own right, common drugs for the treatment of chronic, mainly neuropathic, pain, even though their efficacy is limited. Research in this field has evolved substantially in recent years but there are still many issues to be elucidated in both preclinical and clinical research. From a clinical viewpoint, consistent criteria are required for selection of the type of antidepressant to be used, in addition to the dosage, depending on symptoms, pain type and severity. These criteria could be obtained by using a mechanism-based classification of neuropathic pain that requires clinicians to explore which mechanisms are present in their patients so that they can use this information to optimize the treatment according to the specific mechanisms.

From a preclinical viewpoint, the design of new antidepressant drugs must take into account the pharmacological profile so that the drugs can be used more easily as analgesics once they are marketed. For this, research into the mechanisms of analgesic action of the current antidepressants is first required, including studies of monoamine involvement (especially 5-HT), but also their mechanisms of action on other molecular targets. Such

studies could help to design new antidepressants or drug combinations with an improved efficacy in chronic non-nociceptive pain management.

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