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Antidepressants for the Treatment of Chronic Pain

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Abstract

Chronic pain represents one of the most important public health problems and, in addition to classical analgesics, antidepressants are an essential part of the therapeutic strategy. This article reviews available evidence on the efficacy and safety of antidepressants in major chronic pain conditions; namely, neuropathic

pain, headaches, low back pain, fibromyalgia, irritable bowel syndrome (IBS) and cancer pain. Studies, reviews and meta-analyses published from 1991 to March 2008 were retrieved through MEDLINE, PsycINFO and the Cochrane database using numerous key words for pain and antidepressants. In summary, evidence supports the use of tricyclic antidepressants in neuropathic pain, headaches, low back pain, fibromyalgia and IBS. The efficacy of the newer serotonin and norepinephrine reuptake inhibitors is less supported by evidence, but can be recommended in neuropathic pain, migraines and fibromyalgia. To date, evidence does not support an analgesic effect of serotonin reuptake inhibitors, but beneficial effects on well-being were reported in several chronic pain conditions. These results are discussed in the light of current insights in the neurobiology of pain, the reciprocal relationship between pain and depression, and future developments in this field of research.

1. Chronic Pain

1.1 Aetiology and Diagnostic Categories of Chronic Pain

On the basis of aetiology and neurobiological mechanisms, the following different types of pain can be distinguished:[1-3] (i) nociceptive pain, caused by any lesion or potential tissue damage; (ii) inflammatory pain, due to inflammatory processes; and (iii) neuropathic pain, induced by a lesion or disease affecting the somatosensory system.[4] In the absence of a neurological disorder or peripheral tissue abnormality, the concept of a fourth pain category (functional/dysfunctional pain) has been introduced, supported by the existence of an abnormal central operation of inputs leading to pain hypersensitivity (e.g. in irritable bowel syndrome [IBS], fibromyalgia, tension headache).[5-8] In chronic pain syndromes, the activation of multiple pathophysiological mechanisms leads to a shift towards hyperexcitability of the somatosensory system. However, the distinction of different pain types remains relevant for mechanism-based pain assessment and management. All types of pain respond to some degree to a variety of medications, for example, inflammatory pain responds best to NSAIDs, while neuropathic pain syndromes are most effectively treated by antidepressants and anticonvulsants. However, clinical studies (with the exception of studies on neuropathic pain, which is more homogeneous in terms of aetiology) rarely focus on specific pain categories. For example, in 'low back pain' and 'cancer pain' different pain mechanisms co-exist, in studies on 'headaches' different types are not distinguished and in 'functional/dysfunctional pain' the aetiological mechanism cannot clearly be identified. This makes it difficult to analyse and comment the literature on the efficacy of antidepressants in chronic pain.

1.2 Chronic Pain and Context: Psychosocial Aspects

Another difficulty lies in the fact that pain, and especially chronic pain, is not a pure nociceptive, physical experience, but involves different dimensions of humans, such as affect, cognition, behaviour or social relations. Therefore, the chronic pain experience has to be conceptualized as a convergence of multiple, activated systems with reciprocal influences.[9] This is, for example, illustrated by the influence of pain interpretation on pain perception, the association between pain and depression, the importance of neurotransmitters and psychotropic medication in chronic pain, the benefits of non-pharmacological interventions or the so-called placebo and nocebo effects in the pain experience.[10] In line with these observations, the International Association for the Study of Pain[11] has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Therefore, a

patient with chronic pain is best treated when none of these aspects are neglected in the assessment and management. Such an approach requires a trusting patient-physician relationship, which again depends on an empathic and thoughtful attitude of the clinician who faces patients who are often hopeless, deceived or angered by the limitations of medical power, and project on the physicians a variety of often unrealistic expectations. Although crucial for therapeutic outcome, these elements are not identified as confounding variables in studies on the efficacy of antidepressants for chronic pain, which makes it again difficult to interpret the available data.

2. Neurobiology of Pain and Analgesic Action of Antidepressants

2.1 Pain Mechanisms on Different Neuronal Levels and Role of Antidepressants

The perception of a noxious stimulus, a process referred to as nociception (nociceptive pain), is the result of the activation of a complex neuronal network that is subjected to strong loops of autoregulation and rapid neuroplastic changes. Firstly, highly specialized primary sensory neurons called nociceptors are excited by noxious temperature, intense pressure or irritant chemicals by the opening of ion channel transducers located at the peripheral endings in the skin, viscera, bones, etc. Many transducers have been identified, such as the transient receptor potential vanilloid 1 (TRPV1), which is activated by heat and capsaicin (the pungent ingredient in hot chilli pepper).[12] If the activation is sufficient, it will drive the opening of voltage-gated sodium channels (VGSCs) and the generation of action potentials, while potassium channels will contribute to the repolarization of the cell. Some isoforms of VGSCs are unique to the peripheral nervous system (e.g. Nav1.7, Nav1.8, Nav1.9), but, to date, there are no specific pharmacological blockades of pain-related subunits that can be used in the clinical setting.[13]

In inflammatory pain, the peripheral terminals of nociceptors are subjected to major changes in their chemical environment leading to peripheral sensitization. The numerous inflammatory mediators (prostaglandins, cytokines, bradykinin, amines, neurotrophic factors, etc.) can directly sensitize the terminal in a way that it becomes more receptive. For instance, when exposed to 'inflammatory soup', the TRPV1 channel reduces its opening threshold to 37 C and leads to a burning sensation. Also, at the periphery, prostaglandin (PG)E_2, via the induction of the rate-limiting enzyme cyclo-oxygenase-2, is increased and represents the target for the peripheral analgesic action of NSAIDs. Antidepressants do not prevent peripheral sensitization, but amitriptyline (and, to a lesser extent, fluoxetine) may reduce peripheral PGE_2-like activity or tumour necrosis factor production.[14-16] Blockade of peripheral noradrenergic receptors by tricyclic antidepressants (TCAs) may contribute to a peripheral analgesic action because peripheral release of noradrenaline (norepinephrine) and serotonin is known to be hyperalgesic[15] (see table I).

Hyperexcitability and ectopic activity is unique to neuropathic pain. Altered membrane excitability and abnormal electrogenesis result, in part, from modulation of the VGSC.[13,17,18] The increased excitability leads to the generation of inappropriate action potentials and repetitive firing without a peripheral stimulus. Sodium channel blockade (at the same level as local anaesthetics act) could be considered at high plasma concentrations as a key in the effect of TCAs on neuronal excitability.[19-23] To a lesser extent, fluoxetine and venlafaxine can block VGSCs (at another site of the channel than local anaesthetics/TCAs), whereas, for instance, duloxetine does not.[24-27]

2.2 Spinal Cord, the Brain and Ascending/Descending Pathways

The central terminal of the nociceptor forms synapses with neurons of the superficial dorsal horn of the spinal cord. Although many chemical mediators are released, glutamate is the principal neurotransmitter. Presynaptic release of glutamate acts on postsynaptic receptors present in (i) the projection cells whose axons convey information to various parts of the brain; and (ii) interneurons (both inhibi-

Table I. Suggested mechanisms of action of antidepressants in relation with persistent pain signalling

Mechanism of action	Site of action	TCA	SNRI	SRI
Reuptake inhibition of	Serotonin	+	+	+
monoamine	Noradrenaline	+	+	–
Receptor antagonism	α-Adrenergic	+	–	–
	NMDA	+	(+) milnacipran	–
Blocker or activator of ion channels	Sodium channel blocker	+	(+) venlafaxine – duloxetine	(+) only fluoxetine
	Calcium channel blocker	+	?	(+) citalopram fluoxetine
	Potassium channel activator	+	?	–
$GABA_B$ receptor	Increase of receptor function	+ amitriptyline desipramine	?	+ fluoxetine
Opioid receptor binding/ opioid-mediated effect	- and δ-Opioid receptor	(+)	(+) venlafaxine	(+) paroxetine
Inflammation	Decrease of PGE_2 production	+	?	+ fluoxetine
	Decrease of TNFα production	+	?	?

PGE_2 = prostaglandin E_2; **SNRI** = serotonin and norepinephrine reuptake inhibitor; **SRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant; **TNF**α = tumour necrosis factor-α; + indicates mechanism of action documented *in vitro* and/or *in vivo*; (+) indicates mechanism of action documented *in vitro* and/or *in vivo* at high concentration; – indicates no known mechanism of action; ? indicates not investigated/not known.

tory and excitatory) that all contribute to the local modulatory circuit in the spinal cord. The ascending pathways distribute spinal action potential to brain areas related to the two dimensions of pain perception, sensory and affective: the somatosensory cortex, the periaqueductal grey, the hypothalamus and the amygdala. Spreading from central projections, corticolimbic pathways are also activated. These include the anterior cingulated cortex, the insula and prefrontal cortex regions.

This interconnection between pain and activation of areas involved in the emotional process suggests a neurobiological substrate responsible for the reciprocal relationship between chronic pain and affective disorders (e.g. anxiety and depression). Recently, functional neuroimaging studies have shown that chronic pain impairs several cortical regions. In addition, in experimental models of inflammatory and neuropathic pain, neuroplastic changes have been observed in the amygdala or the anterior cingulated cortex.[28-33]

Descending inhibitory or facilitatory pathways from supraspinal sites (mainly the hypothalamus, anterior cingulated cortex and amygdala via the periaqueductal grey and the rostral ventromedial medulla) converge at the dorsal horn, controlling the peripheral input from the nociceptor and probably contribute to placebo and nocebo effects. The anticipation of an analgesic treatment may drive complex inhibitory descending outputs and lead to placebo analgesia; in contrast, negative verbal suggestion, for instance, may modulate facilitatory processes and result in exacerbation of the painful stimulus, the nocebo effect.[34] Top-down opioidergic and monoaminergic neurons (serotonin and noradrenaline) from descending pathways have complex and fragile modes of action.[35] It has been suggested that in neuropathic pain, in particular, an increase in descending facilitatory pathway and a reduction in inhibitory ones, underlies the chronic pain state.[30,36] The main effect of antidepressants is thought to be on the reinforcement of descending inhibition by increasing the amount of noradrenaline and serotonin in the synaptic clefts at supraspinal and spinal levels.

2.3 The Dorsal Horn

The superficial laminae of the spinal cord are the site of convergence of peripheral input and descending pathways. As a result of the action of inhibitory molecules (GABA, endogenous opioids, monoamines), the spinal cord controls the transmission of

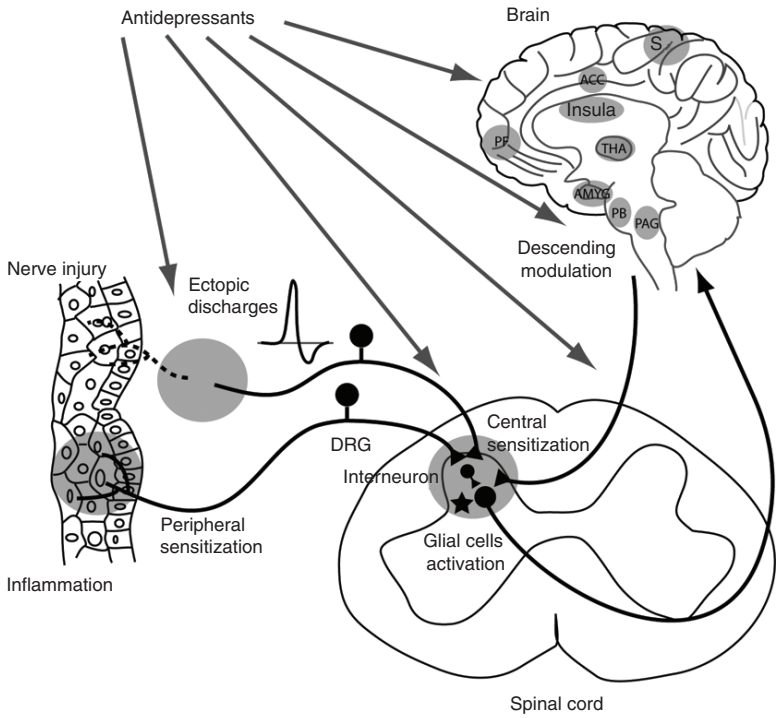

Fig. 1. Schematic illustration of the main structures of the nervous system involved in pain perception, and pathological mechanisms related to inflammatory and neuropathic pain. Sites of actions of antidepressants are suggested to be centrally mediated by the reinforcement of descending pathways and inhibition at spinal, brain stem and brain levels. Peripheral effects on the nociceptors have also been demonstrated. **ACC** = anterior cingulated cortex; **AMYG** = amygdala; **DRG** = dorsal root ganglia; **PAG** = periaqueductal grey; **PB** = parabrachial nucleus; **PF** = prefrontal cortex; **S** = somatosensory cortex; **THA** = thalamus.

noxious stimuli. Only a small fraction of a noxious input from the periphery will initiate output to the brain (see figure 1).

The central terminal of the nociceptor is a major site of the so-called presynaptic action of opioids, GABA receptor ligands, and gabapentin and pregabalin. The latter are believed to act on the $\alpha 2\delta$ subunit of VGSCs to reduce excitatory transmitter release. Postsynaptic inhibition (the action is on the dorsal horn neuron) involves mainly opioids and GABA. A potential boost of inhibition can be related to the enhanced GABA receptor function induced by TCAs and serotonin reuptake inhibitors (SRIs). The effect of monoamines (which is increased by reuptake inhibition with antidepressants) is acting on serotonin and noradrenline (α_2 adrenoceptors) receptors, which have been identified in inhibitory interneurons, excitatory interneurons and projection neurons, resulting in a pre- and post-synaptic action.[35,36] In addition, binding to opioid receptors has been reported for almost all TCAs, the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine and the SRI paroxetine, but some authors suggest the affinity is probably too low to act at therapeutic drug concentrations.[37-39] TCAs are also calcium channel antagonists, which may account for an additional analgesic role of TCAs.[40,41]

Central sensitization, a key mechanism involved in the persistence of pain, is triggered by intense activation of nociceptors, as well as by humoral factors released by the inflamed peripheral tissue.[42] The action of excitatory transmission is augmented by increased release of neurotransmitters and augmented function of post-synaptic receptors, such as the glutamate receptor NMDA. Hours and days after injury, the pain signal can remain sustained by tran-

scriptional changes in the dorsal horn, including induction of PGE_2 production, which, in turn, facilitates excitatory and reduces inhibitory transmission. The changes, restricted to the activated synapse or spread to adjacent synapses, are responsible for pain produced by low-threshold afferent inputs (allodynia) and pain in regions beyond the tissue injury (secondary hyperalgesia).

After nerve injury, the amount of input produced by peripheral ectopic activity, in addition to changes in gene expression, will contribute to central sensitization. Surrounding non-neuronal cells, the microglia and astrocytes, are activated and modify the interaction with the neurons and release various molecules contributing to local neuroinflammation and pain hypersensitivity.[43-45] Alteration of synaptic connectivity together with cell death (mainly of inhibitory interneurons) will result in permanent disinhibition and possibly irreversible changes in the nervous system.[46]

By boosting inhibition, antidepressants may counteract disinhibition, but their action may also contribute to other mechanisms such as blockade of the NMDA receptor.[47]

2.4 Summary

In summary, chronic pain is the result of a complex molecular and structural reorganization of the nervous system. While identification of new mechanisms will lead to new therapeutic options, TCAs and SNRIs will remain very useful. Overall, TCAs could be more effective than SNRIs or SRIs because of their various effects at central and peripheral sites (especially VGSC blockade). TCAs, and amitriptyline in particular, are the most studied; however, new research on SNRIs may reveal new mechanisms of action. From a mechanism-based perspective, it is interesting to note that at therapeutic concentrations, all antidepressants have a very restricted or no effect on nociception, which indicates that these drugs are more likely to restore the normal function of an altered pain system than to inhibit normal pain transmission.

3. Efficacy of Antidepressants in Specific Chronic Pain Conditions

An extensive literature search was performed on MEDLINE, PsycINFO and the Cochrane database to retrieve controlled studies, review articles and meta-analyses published from 1991 to March 2008. Numerous (36) key words were used for chronic pain conditions (e.g. migraine, neuropathic pain, fibromyalgia) and type of antidepressants (e.g. TCA, SRI, SNRI, thymoleptic). For each chronic pain condition, we report the results of most recent meta-analysis, as well as additional randomized controlled trials (RCTs) subsequently published.

3.1 Neuropathic Pain

3.1.1 Peripheral Neuropathic Pain

Neuropathic pain is characterized by somatosensory changes in the innervation territory corresponding to peripheral or central nervous system pathology, and the paradoxical occurrence of pain and hypersensitivity phenomena within the denervated zone and its surroundings.[48] Peripheral neuropathic pain is the best studied pain condition for the therapeutic use of antidepressants. Most RCTs have been conducted in postherpetic neuralgia and painful polyneuropathy (PPN), essentially diabetic polyneuropathy. Different types of peripheral neuropathic pain show similar outcome, except HIV- and chemotherapy-induced neuropathy, which do not appear to respond to antidepressants (see section 3.1.2). According to a recent Cochrane meta-analysis[49] (see table II), which included 61 studies, TCAs are considered to be efficient in neuropathic pain on the basis of sufficient class I trials[2,50-92] (see table II).

Overall, the number needed to treat (NNT) for effectiveness of TCAs was 3.6 (95% CI 3, 4.5). Amitriptyline, the most frequently studied balanced serotonergic and noradrenergic TCA (ten studies), was found to have a NNT of 3.1 (95% CI 2.5, 4.2) in doses of up to 150 mg/day, and imipramine was found to have a NNT of 2.2 (95% CI 1.7, 3.2). The noradrenergic TCA desipramine was found to have a NNT of 2.6 (95% CI 1.9, 4.5). Data on SRIs

Table II. Studies on the use of antidepressants in neuropathic pain

Publication (year)	No. of patients	Antidepressant	Study arms	Outcome	NNT (95% CI)	References
Meta-analysis						
Saarto and Wiffen[49] (2007) [1966–2005]	3293 (in 61 studies)	TCAs: amitriptyline, desipramine, imipramine, clomipramine, nortriptyline, doxepin, mianserin, maprotiline	31 TCA vs PL 12 TCA vs TCA 13 TCA vs other ttt	TCAs > PL	TCA: 3.6 (CI 3, 4.5)	2,50-92
		SRIs: citalopram, fluvoxamine, paroxetine, fluoxetine, sertraline	4 SRI vs PL 2 SRI vs TCA 1 SRI vs SRI 1 SRI vs other ttt	SRI > PL SRI < TCAs	NA	73,80,93-95
		SNRI: venlafaxine	5 SNRI vs PL 1 SNRI + gabapentine vs PL 1 SNRI vs TCA	SNRI > PL	Venlafaxine: 3.1 (CI 2.2, 5.1)	69,75,96-99
Additional studies since 2005						
Goldstein et al.[100] (2005)	457	SNRI: duloxetine	Duloxetine vs PL	SNRI > PL	NA	100
Raskin et al.[101] (2005)	348	SNRI: duloxetine	Duloxetine vs PL	SNRI > PL	NA	101
Wernicke et al.[102] (2006)	334	SNRI: duloxetine	Duloxetine vs PL	SNRI > PL	NA	102

NA = no available NNT due to insufficient data; **NNT** = number needed to treat; **PL** = placebo; **SNRI** = serotonin and norepinephrine reuptake inhibitor; **SRI** = serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant; **ttt** = treatment; > indicates more effective than; < indicates less effective than.

(citalopram, fluvoxamine, paroxetine, fluoxetine, sertraline) are limited.[73,80,93-95] SRIs, compared with placebo in only four studies, were found to be superior to placebo, but evidence was insufficient to calculate robust NNT. Two additional studies, which compared SRIs to TCAs, found SRIs to be less efficient than TCAs. Among the newer antidepressants, the SNRI venlafaxine was evaluated in seven studies[69,75,96-99] in doses ranging from 75 to 225 mg/day and achieving a NNT of 3.1 (95% CI 2.2, 5.1), similar to values seen with TCAs. The previously mentioned meta-analysis[49] also calculated NNT for main neuropathic conditions: in diabetic neuropathy (13 studies), the overall NNT for effectiveness compared with placebo was 1.3 (95% CI 1.2, 1.5), whereas in post-herpetic neuralgia (six studies), the overall NNT for effectiveness was 2.7 (95% CI 2, 4.1). Depression was studied in 18 studies included in this meta-analysis, and it appeared that there was no correlation between depression and pain relief. However, the meta-analysis did not include three recently published studies with the SNRI duloxetine;[100-102] a *post hoc* analysis[103] of these three placebo-controlled studies found that patients receiving duloxetine 60 mg once daily had a NNT of 5.2 (95% CI 3.8, 8.3) and those receiving duloxetine 60 mg twice daily a NNT of 4.9 (95% CI 3.6, 7.6).

All recent evidence-based guidelines[21,104,105] confirm that TCAs have established efficacy in neuropathic pain and consider them (in particular amytriptyline) as first-choice treatment along with gabapentine and pregabalin. It is also proposed that the SNRIs venlafaxine and duloxetine should be second-choice treatments in painful neuropathy.[105] In the elderly and in patients with cardiovascular risk factors, it is suggested that SNRIs should be preferred to TCAs given the cardiovascular adverse effects of TCA. All reviews agree that there are insufficient data on the effectiveness of SRIs in neuropathic pain.[49,105]

3.1.2 Neuropathic Pain not Relieved by Antidepressants

Negative trials are difficult to interpret and no final statement can be made on specific neuropathic

pain conditions not responding to antidepressants. The literature reports trials that do not support the use of antidepressants in pain related to spinal cord injury, phantom limb, chemotherapy and HIV neuropathy.[51,55,64,68,70,106,107]

3.1.3 Central Neuropathic Pain

Central neuropathic pain can be caused by a stroke, a spinal cord injury, multiple sclerosis or other aetiologies. The efficacy of antidepressants is far less documented than in peripheral neuropathic pain and relies on a few studies with small sample sizes. In post-stroke pain, amitriptyline was found to be superior to placebo and to carbamazepine.[59] In contrast, amitriptyline was not superior to placebo in another study on spinal cord injury patients.[51] Recent guidelines on neuropathic pain consider that there is level B evidence for the use of TCAs in central neuropathic pain.[105]

One of the difficulties in comparing studies is the variety of ways pain outcome was measured – this tends to have improved in more recent trials.[75,100,101] Also, the effect of antidepressants on aspects other than pain, such as quality of life (QOL), has rarely been studied; a recent study with duloxetine, for example, showed clear improvement of QOL in PPN patients.[100]

3.2 Headaches

Tomkins et al.[108] incorporated studies of all classes of antidepressants in migraine and tension-type headache in a recent meta-analysis, including 19 evaluating TCAs[109-125] (12 of them amytriptyline), 18 serotonin receptor antagonists[126-140] and 7 SRIs[141-146] (see table III). The main conclusion was that patients treated with antidepressants were twice as likely to improve than those treated with placebo, and that the overall NNT was 3.2 (95% CI 2.5, 4.3). Separate meta-analyses showed a similar improvement for migraine and tension headache, but not significant differences for different types of antidepressants (beneficial effects of TCAs were strongest). Accordingly, current recommendations consider amitriptyline as a recommendation level I drug,[147,148] with a therapeutic dosage ranging from 30 to 150 mg/day.

Table III. Studies on the use of antidepressants in headaches

Study (year)	No. of patients	Antidepressant	Study arms	Outcome	NNT (95% CI)	References
Meta-analysis						
Tomkins et al.[108] (2001)	1882 (in 38 studies)	TCA: amitriptyline, opipramol, clomipramine, doxepin, maprotiline	19 arms (12 arms with amitryptyline)	Migraine and tension-type headache: AD > PL	AD: 3.2 (2.5, 4.3)	109-125
		Serotonin blockers: pizotifen, pizotyline, mianserin	18 arms			126-140
		SRI: fluvoxamine, citalopram, fluoxetine, femoxetine	7 arms			141-146
Moja et al.[149] (2005)	635 (in 13 studies)	SRI: fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram	5 SRI vs PL 8 SRI vs another AD	Migraine and tension-type headache: SRI = PL	NA	120,144,145,150-1
Additional studies since 2001						
Bendtsen and Jensen[158] (2004)	24	NaSSA: mirtazapine	Mirtazapine vs PL	Tension-type headache: mirtazapine > PL	NA	158
Bulut et al.[159] (2004)	52	SNRI: venlafaxine	Crossover trial: venlafaxine-amitryptiline	Migraine: venlafaxine = amitryptiline	NA	159
Ozyalcin et al.[160] (2005)	60	SNRI: venlafaxine	Venlafaxine vs PL	Migraine: venlafaxine > PL	NA	160

NA = no available NNT due to insufficient data; **NaSSA** = noradrenergic and specific serotoninergic antidepressant; **NNT** = number needed to treat; **PL** = placebo; **SNRI** = serotonin and norepinephrine reuptake inhibitor; **SRI** = serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant; > indicates more effective than; = indicates as effective as.

The efficacy of SRIs in migraine and tension headache was re-examined in a recent Cochrane review[149] that identified 13 studies comparing SRIs with placebo and other antidepressants[120,144,145,150-157] for the prevention of migraine or tension-type headache. This meta-analysis showed that SRIs did not significantly reduce headache global severity index in patients when compared with placebo after 8 weeks of treatment. Moreover, none of the other main outcome measures (headache frequency, severity and duration) or secondary outcomes, such as tolerability, use of other analgesics, QOL and mood, significantly favoured SRIs. Therefore, to date, evidence does not support the use of SRIs in migraine or tension-type headache. However, given the limited number of studies, their small sizes and short follow-up duration, as well as methodological limitations, such as the various scales used in the different studies, there is a need to further investigate the effects of SRIs in these conditions.

Recent studies evaluating newer antidepressants (e.g. mirtazapine, venlafaxine) were not included in the previously mentioned meta-analysis.[108] One RCT with short follow-up duration found comparable effectiveness between amitriptyline and the noradrenergic and specific serotonergic antidepressant mirtazapine for the treatment of chronic tension-type headache. Another small placebo-controlled trial found that mirtazapine significantly reduces frequency, duration and intensity of headache.[158] Two trials with the SNRI venlafaxine also showed a benefit in migraine headaches.[159,160] In a placebo-controlled trial with venlafaxine 75 or 150 mg/day, the higher dose was effective in reducing the frequency of migraine attacks, while being well tolerated.[160] When comparing venlafaxine and amitriptyline,[159] both drugs were found to have similar effects in the prophylactic treatment of migraine. We did not find a study using the SNRI duloxetine.

3.3 Low Back Pain

Low back pain (LBP) affects more than two-thirds of people at some time in their life and is one of the most common reasons for seeking medical care. Persistent LBP of severe intensity is reported in about 5–10% of individuals.[161] While several types of pathophysiological mechanisms are involved in LBP (neuropathic, inflammatory, mechanical or central), this aetiological heterogeneity is not taken into account in studies evaluating the effects of antidepressants.

In spite of the high prevalence of LBP and the limited therapeutic options, there are only a few RCTs with antidepressants and all are of limited follow-up duration (4–8 weeks). One meta-analysis,[162] one systematic review[163] and a recent study[164] provide relevant data on the effect of antidepressants on chronic LBP (see table IV).

In their meta-analysis, Salerno et al.[162] included nine RCTs that were considered as being of moderate quality. Seven studies used hetreocyclics and tricyclic compounds (amitriptyline, imipramine, nortriptyline, desipramine, doxepin, maprotiline, trazodone)[165-172] and the two other studies used the SRI paroxetine.[171,173] Overall, the results showed that antidepressants had a small but statistically significant effect in reducing pain when compared with placebo (standardized mean difference 0.41; 95% CI 0.22, 0.61). The five trials that measured global functioning showed a trend in improving activities of daily living. In a subsequent high quality systematic review, Staiger et al.[163] evaluated variance of outcomes between the classes of antidepressants. The same set of studies was considered as those in Salerno et al.,[162] with the exception of two studies, which were excluded because they treated both neck pain and LBP patients. The authors found that antidepressants that inhibit norepinephrine reuptake (amitriptyline, imipramine, nortriptyline, maprotiline)[165,166,169-171] are mildly to moderately effective in reducing pain (only one of the five trials of shorter duration was negative). In the three studies with compounds that do not inhibit norepinephrine reuptake (trazodone, paroxetine),[171-173] no analgesic benefit was observed. The authors concluded that the impact of medications on functional status remains unclear. Since these reviews were published, one placebo-controlled trial investigating the use of the norepinephrine and dopamine reuptake inhibitor (NDRI) bupropion, found no evidence of

Table IV. Studies on the use of antidepressants in low back pain

Publication (year)	No. of patients	Antidepressant	Study arms	Outcome	NNT	References
Meta-analysis						
Salerno et al.[162] (2002) [1966–2000]	504 (in 9 studies)	TCA: amitriptyline, imipramine, nortriptyline, desipramine, doxepine, maprotiline	7 TCAs vs PL	AD > PL	NA	165-171
		SARI: trazodone	1 SARI vs PL			172
		SRI: paroxetine	2 SRI vs PL			171,173
Additional systematic reviews and studies since 2002						
Staiger et al.[163] (2003)	450 (in 7 studies)	TCA: amitriptyline, imipramine, nortriptyline, maprotiline	5 TCAs vs PL	TCAs > PL	NA	165,166,169-171
		SARI: trazodone	1 SARI vs PL	SARI = PL	NA	172
		SRI: paroxetine	2 SRI vs PL	SRI = PL	NA	171,173
Katz et al.[164] (2005)	44	NDRI: bupropion	Bupropion vs PL	Bupropion = PL	NA	164

NA = no available NNT due to insufficient data; **NDRI** = norepinephrine and dopamine reuptake inhibitor; **NNT** = number needed to treat; **PL** = placebo; **SARI** = serotonin antagonist reuptake inhibitor; **SRI** = serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant; > indicates more effective than; = indicates as effective as.

efficacy in patients with chronic LBP.[164] No RCTs were found for the SNRIs duloxetine or venlafaxine.

These studies confirm the statement of the most recent guideline of the American Pain Society and American College of Physicians[174] that there is good evidence that TCAs are effective for pain relief with a magnitude of benefit being small to moderate. The effects on functional outcomes are inconsistently reported and evidence does not indicate a clear benefit. The few trials using SRI (paroxetine), serotonin antagonist reuptake inhibitor (trazodone) or NDRI (bupropion) are negative (see table IV).

3.4 Fibromyalgia

Fibromyalgia is a chronic musculoskeletal pain disorder of unknown aetiology, characterized by widespread pain and muscle tenderness, often accompanied by fatigue, sleep disturbance and depressed mood.[175] Evidence indicates abnormalities in central monoaminergic neurotransmission with a possible dysfunction in both the serotonin and norepinephrine systems.[176,177] Decreased central -opioid receptor availability was also recently suggested.[6] Two recent meta-analyses include mainly trials with TCAs,[178,179] whereas a few more recent studies investigated the use of SNRIs (see table V).

The meta-analysis by Arnold et al.[178] included nine placebo-controlled trials with TCAs (amitriptyline, dosulepin [dothiepin], cyclobenzaprine).[180-187] Significant clinical response to TCAs was observed in about 30% of patients, with all outcomes improved (self-ratings of pain, stiffness, fatigue, sleep, patient and physician global assessment of improvement, and tenderness of tender points). Overall, degree of efficacy was modest (best for sleep, weakest for tender points). The meta-analysis by O'Malley et al.[179] included 13 placebo-controlled trials, nine with TCAs (amitriptyline, cyclobenzaprine, clomipramine, maprotiline),[180,184,187-191] an additional three small studies with SRIs (citalopram, fluoxetine)[192-194] and two with adenetionine (*S*-adenosylmethionine).[195,196] They found that patients treated with antidepressants significantly improved compared with those receiving placebo and that the overall NNT was 4

Table V. Studies on the use of antidepressants in fibromyalgia

Study (year)	No. of patients	Antidepressant	Study arms	Outcome	NNT (95% CI)	References
Meta-analysis						
Arnold et al.[178] (2000)	585 (in 9 studies)	TCA: amitriptyline, dosulepin, cyclobenzaprine	9 TCA vs PL	TCA > PL	NA	180-187
O'Malley et al.[179] (2000)	700 (in 13 studies)	TCA: amitriptyline, cyclobenzaprine, clomipramine, maprotiline	9 TCA vs PL	AD > PL	AD: 4 (2.9, 6.3)	180,184,187-191
		SRI: citalopram, fluoxetine	3 SRI vs PL			192-194
		Ademetionine	Ademetionine vs PL			195,196
Additional studies since 2000						
Arnold et al.[197] (2002)	60	SRI: fluoxetine	Fluoxetine vs PL	Fluoxetine > PL	NA	197
Gendreau et al.[198] (2005)	125	SNRI: milnacipran	Milnacipran vs PL	Milnacipran > PL	NA	198
Arnold et al.[199] (2004)	207	SNRI: duloxetine	Duloxetine vs PL	Duloxetine > PL	NA	199
Arnold et al.[200] (2005)	354	SNRI: duloxetine	Duloxetine vs PL	Duloxetine vs PL	NA	200
Russell et al.[201] (2008)	520	SNRI: duloxetine	Duloxetine vs PL	Duloxetine > PL	NA	201

NA = no available NNT due to insufficient data; **NNT** = number needed to treat; **PL** = placebo; **SNRI** = serotonin and norepinephrine reuptake inhibitor; **SRI** = serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant; > indicates more effective than.

(95% CI 2.9, 6.3). Improvement in pain scores, sleep, well-being and fatigue was also reported, but no improvement in trigger points was seen. There was no correlation between the effect on depression or anxiety and these outcomes in either meta-analysis.

On the basis of these data, recent guidelines conclude that TCAs may be considered as effective in fibromyalgia (e.g. amitriptyline 25–50 mg at bedtime).[186,202] Very limited and inconsistent results were obtained with SRIs in fibromyalgia. Only fluoxetine (20–80 mg/day, mean dose 45 mg/day) was found to be superior to placebo in a study with 60 female patients in improving pain, fatigue and depression, but not number of tender points,[197] whereas fluoxetine 20 mg/day[193] or citalopram 20–40 mg/day[192] were not superior to placebo.

Recent studies have reported positive results with the SNRIs. Arnold and colleagues,[199] in a 12-week, multicentre RCT with duloxetine in 207 female patients with fibromyalgia, reported significant improvement in pain severity, tender point count and sensitivity, stiffness and QOL. These changes were observed independently of the presence of co-morbid depression. Male patients did not show significant improvement on any of the outcome measures, but represented only 10% of the sample. In a subsequent study,[200] 354 patients were randomized to one or two doses of duloxetine (60 mg either once or twice daily) or placebo. Both duloxetine groups demonstrated greater improvement in pain severity than placebo and this effect was independent of changes in mood. More than half of the participants randomized to duloxetine experienced >30% improvement in pain compared with one-third of those in the placebo group. No differences in outcomes were observed between the two doses, except that only the duloxetine 60 mg twice-daily dose, compared with placebo, significantly improved the tender point assessments. This is notable because previous fibromyalgia studies using TCAs found minimal improvement in tender point measures. The most recent study with duloxetine was of longer duration and confirmed a beneficial effect of duloxetine at 60 or 120 mg/day on reduction in pain both

at 3 and 6 months follow-up.[201] Other outcome measures such as clinical global improvement, mental fatigue and QOL, were also significantly improved in the duloxetine groups compared with placebo. In contrast with the previous studies, there were no sex differences and no improvement in tender point threshold. On the basis of these data, the US FDA approved duloxetine for the treatment of fibromyalgia in 2008.

Milnacipran, another dual reuptake inhibitor, was examined in 125 patients with fibromyalgia.[198] After 12 weeks, the twice-daily milnacipran (dose escalation up to 200 mg/day) group showed significantly greater improvement on measures of pain intensity, fatigue, morning stiffness, physical function and global well-being compared with placebo. Accordingly, current recommendations consider milnacipran as possible second-line drug treatments for fibromyalgia.[186,202] We did not identify any placebo-controlled study with venflaxine in fibromyalgia.

3.5 Irritable Bowel Syndrome

IBS is a chronic gastrointestinal disorder characterized by recurrent episodes of abdominal pain and altered bowel habits, such as diarrhoea or constipation. The pathophysiological pathway of IBS is unknown, but it is assumed that symptoms are mediated by the brain-gut axis. It is estimated that 50–90% of patients with IBS have a psychiatric comorbidity such as anxiety disorders or depression.[203] To date, there is no clear evidence of benefit for antidepressants in IBS. One meta-analysis[204] including 11 studies on functional gastro-intestinal disorders (nine used TCAs[205-213] and two used mianserin[205,214]), of which eight consisted of patients with IBS exclusively, found a significant effect for global assessment and abdominal pain, with a NNT of 3.2 (95% CI 2.1, 6.5). However, a more recent Cochrane review on treatments of IBS,[215] using more restrictive criteria for study inclusion, did not demonstrate any benefit for antidepressants for global assessment or for abdominal pain. In the limited number of available studies, beneficial effects on pain were observed with low dose of TCA,[204] whereas in the very few trials using SRIs (fluoxetine, paroxetine, citalopram),[216-218] a possible improvement in well-being of patients with IBS was reported, but few, if any, effects on pain and bowel symptoms.[219]

3.6 Cancer Pain

Cancer pain is very frequent, especially in advanced stages of the disease, where up to 75–90% of patients experience moderate to severe pain.[220] Many different causes may lead to cancer pain including visceral tumour infiltration, bone metastases and chemotherapy-induced neuropathy.[221] Antidepressants are considered as adjuvant analgesics, along with antiepileptics and corticosteroids in evidence-based guidelines, and are proposed in patients how have unsatisfactory responses to minor or major analgesics (i.e. NSAIDs and opioids).[222,223] In spite of these guidelines, a large survey found that such adjuvant analgesics are rarely used by physicians even in cases of unresponsiveness to conventional analgesics.[224] Surprisingly, there are almost no controlled trials assessing the effect of antidepressants in cancer pain. While antidepressants are considered in the already discussed referenced literature article to be useful, especially in neuropathic pain, only two controlled trails studied the efficacy of TCAs in chemotherapy-induced neuropathic pain,[106,107] and both studies were negative. A study with nortryptiline found no difference compared with placebo,[106] whereas a more recent study with amytriptyline found no effect on pain, but significant improvement in QOL.[107] Both studies where small and used very low doses of TCAs (nortryptiline 100 mg/day; amytriptyline 50 mg/day). We found no controlled studies with SRIs or SNRIs in cancer pain; therefore, their use relies on clinical experience.

4. Chronic Pain and Depression

There is evidence of a high co-morbidity of chronic pain and depression.[225-227] Studies found that as many as 75–80% of patients with depression report painful somatic symptoms, such as headache, stomach pain, neck pain, LBP or non-specific gener-

alized pain.[228] Moreover, studies found that among those with depression, more than 40% experienced chronic pain[229] or pain resulting in functional impairment.[230] On the other hand, patients with chronic pain frequently experience co-morbid depression. For instance 20–40% of patients with fibromyalgia were found to have a co-morbid depression[231] and the prevalence of mood disorder among individuals with spinal pain was found to be 17.5%.[227] In a longitudinal perspective, a large survey found that after adjusting for demographic variables, back pain was the strongest predictor of depression[232] and it was also shown that having a chronic painful medical condition more than doubled the risk of major depression.[233-236]

The high co-morbidity between chronic pain and depression, which should lead clinicians to investigate both dimensions when a patient presents with either pain or depression, must be emphasized because it has been shown that the presence of pain tends to negatively affect the recognition and treatment of depression.[237] Depression of moderate or severe intensity must be treated not only for itself[238] but also because the presence of non-treated depression may lead to poorer treatment outcome and greater levels of disability.[239-241] It is also worth bearing in mind that patients with chronic pain and depression have an increased risk of suicidal behaviour.[242]

From a biochemical point of view, there is evidence of a dysregulation of central monoaminergic neurotransmitters in major depression, including a decrease in serotonin and norepinephrine.[243,244] These neurotransmitters are implicated in pain modulation systems, such as the pain descending inhibitory pathways described in section 2.2, which may explain, in part, why depression appears to predispose to pain symptoms.[237] Moreover, antidepressants that increase levels of serotonin and norepinephrine (e.g. TCAs, SNRIs) are those with proven beneficial effects on pain;[245] therefore, the effect of antidepressants on pain is thought to be mediated through the increase in noradrenaline and serotonin in the synaptic clefts at supraspinal and spinal levels of pain modulating structures.[243]

Despite all this evidence, the presence of co-morbid depression in patients with chronic pain has been largely overlooked, even in studies assessing the effect of antidepressants in chronic pain conditions. When depression was assessed, this was rarely done with appropriate diagnostic instruments. Nevertheless, in studies where depression was evaluated, the effect of antidepressants on pain appeared to be independent of the effect on co-morbid depression. This is certainly true for neuropathic pain,[49] migraine[108] and fibromyalgia,[178,179] but it is somewhat less clear in LBP.[162]

5. Adverse Effects and Interactions of Antidepressants

5.1 General Tolerability of Antidepressants

Placebo-controlled trials assessing the analgesic efficacy of antidepressants in chronic pain conditions confirm adverse reactions in a significant proportion of patients. Patients with chronic pain seem to be more sensitive to adverse effects because they tend to be more concerned and reactive towards somatic symptoms than psychiatric patients.[246] Therefore, a progressive introduction of antidepressants is widely recommended. The ‘start low go slow’ maxim illustrates that the drugs should be introduced at the lowest available dosage and increased by weekly steps until the desired efficacy is achieved, a predefined ceiling dose is reached or dose-limiting adverse effects emerge.

The tolerability profiles of TCAs are linked to their anticholinergic actions, resulting in mouth dryness, constipation and difficulty emptying the bowel or bladder, which can affect more than 60% of patients with chronic pain.[247] In predisposed patients, TCAs may decompensate ocular glaucoma or incomplete bladder occlusion, and are therefore contra-indicated. Other adverse effects such as sedation, drowsiness or orthostatic hypotension are due to the antihistaminic and $\alpha 2$-adrenergic actions of TCAs.[248] The cardiovascular tolerability of TCAs is a problem for patients experiencing various heart diseases, especially the elderly because they may

trigger arrhythmias through direct action on the myocardium.[249,250]

The main adverse effects of SRIs are caused by their interferences with the peripheral and central signalling actions of serotonin, which result in nausea, gastric discomfort, vomiting, anorexia, diarrhoea and hyperhydrosis of the skin.[105] At high circulating concentrations or in cases of drug interaction, SRIs may cause a stormy overactivation of serotoninergic pathways, called 'serotonin syndrome', characterized by intestinal symptoms, fever, motor signs (such as tremor, rigidity and hyperreflexia) and central neuropsychiatric disturbances including anxiety, nervousness, sedation, confusion and delirium.[251] A full-blown serotoninergic syndrome may be life-threatening. The phenomenon is dose-dependent and of variable severity, often developing progressively. Thus, serious outcomes might be prevented by prescribing low doses to start and interrupting treatment in cases of early serotoninergic signs.

Serotoninergic adverse effects are less frequently encountered with TCAs (although most of them inhibit serotonin as well as noradrenalin reuptake), possibly as a result of the masking of anticholinergic activity. Other recently developed antidepressants with mixed noradrenergic and serotoninegic actions, such as venlafaxine and duloxetine, can also trigger characteristic adverse effects as a result of increased central and peripheral serotonin overactivity. Thus, nausea, vomiting, anorexia and hyperhydrosis have been reported to affect up to 40% of patients receiving duloxetine.[252,253] Atypical antidepressants such as mianserin, mirtazapine, trazodone and nefazodone have little risk of inducing serotonin toxicity;[254] however, they are of limited interest in the treatment of chronic pain conditions.

Antidepressants may also induce physical dependence and withdrawal symptoms in cases of abrupt cessation,[255] which may be difficult to differentiate from the symptoms for which the treatment has been introduced.[256] Therefore, providing patients with adequate information and progressively tapering off the doses is recommended.

5.2 Pharmacogenetics and Interaction Potential

All antidepressants undergo extensive liver metabolism, and belong to the class of drugs with intermediate to high hepatic extraction and limited oral bioavailability. The specific liver enzymes ensuring first-pass metabolism and systemic clearance vary between the different agents. The cytochrome P450 (CYP) isoenzyme CYP2D6 is involved to a significant extent for a majority of agents.[257,258] This isoenzyme is well known for its genetic polymorphism, with up to 7% of the Caucasian population having a poor metabolizer phenotype and another 2% an ultrarapid metabolizer phenotype. Moreover, CYP2D6 is sensitive to the inhibiting action of many drugs, while it does not seem to be inducible, unlike other isoenzymes of this family. Many antidepressants are substrates of CYP2D6 and some of them also have an inhibitory activity on this enzyme. Venlafaxine, duloxetine and several SRIs and TCAs are metabolized through CYP2D6, the polymorphism of which explains the remarkable variability in their efficacy and tolerability.[259,260] This represents a further argument to start treatment at low doses and gently titrate the dosage while monitoring the patient's response. The potential role of generalized pharmacogenetic testing and/or blood concentration monitoring as aids to dosage decisions is a matter of debate.[261] In any case, special attention is recommended in patients receiving co-medications that are able to inhibit the CYP2D6, such as terbinafine or quinidine.[262] In addition, some antidepressants are themselves CYP2D6 inhibitors; for example, fluoxetine and paroxetine are known to cause drug interactions with various CYP2D6 substrates (e.g. antiarrhythmic agents, antipsychotics, tegaserod, tamoxifen).

On another hand, some analgesic agents need CYP2D6 for their metabolic bioactivation; for example, codeine, which is known to exert most of its analgesic actions through the conversion of about 10% of the dose into morphine.[263] The administration of CYP2D6 inhibitors can block this reaction and thus suppress the analgesic potency of codeine to a clinically significant extent. Tramadol, an anal-

gesic agent with mixed pharmacological activity, is also transformed into an opioidergic metabolite through CYP2D6, while the native molecule mainly acts by blocking catecholamine reuptake, a mechanism shared with antidepressants, participating to the control of pain. Therefore, the coadministration of tramadol with antidepressants can both increase the risk of exaggerated aminergic stimulation, translating clinically in manifestations of the serotonin syndrome, and decrease the biotransformation of tramadol into morphinomimetic derivatives, depriving the patient from their benefits.[264,265]

Finally, in addition to their pharmacokinetic interactions, antidepressants may further participate in pharmacodynamic interactions. Other classes of drugs can add their own contribution to antidepressant-related risks of serotonin syndrome (e.g. antimigraine agents, cocaine, amphetamines or ecstasy, antibacterials such as linezolid), seizure induction (e.g. antipsychotics, stimulants, alcohol, β-lactam and fluoroquinolone antibacterials, isoniazid, antiasthmatics), ventricular arrhythmias (e.g. antiarrythmic agents, antiepileptics, antipsychotics, methadone, macrolide antibacterials) or gastro-intestinal bleeding (e.g. anti-inflammatory agents, anticoagulants).

6. Future Directions and Conclusions

Preclinical studies have successfully elucidated some of the molecular mechanisms of action of antidepressants and their effects on pain mechanisms. Instead of suppressing pain, TCAs and SNRIs most probably contribute to normalize the function of the nervous system by reducing some of the maladaptive plasticity related to chronic pain states. Currently, pain syndromes are defined by a conventional assessment of pain (causative disease, anatomical referral pattern and quantification of pain intensity), which does not provide any information about whether or not the treatment acts on a particular mechanism (e.g. disinhibtion) or reduces a particular symptom (e.g. tactile allodynia). Because antidepressants have specific mechanisms to counteract pain mechanisms, and pain mechanisms vary in a given cohort of patients, antidepressants produce varied responses. This does not only lead to the risk of missing an analgesic effect, but also that patients may give up on a treatment, which has a high potential for efficacy but only in few patients. There is growing evidence that using comprehensive clinical symptoms to assess pain might lead to a mechanism-based classification of pain and clusters of patients, independent of the causative disease, and thus may improve treatment and predict the efficacy of antidepressants. Increased translational research is, as in other domains of medicine, a key for further improvement of the treatment of chronic pain with antidepressants.

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