Antidepressants in Chronic Neuropathic Pain

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Abstract: This review presents available clinical studies and new insights into mechanisms of analgesic effect and possible new routes of administration of antidepressant drugs. Older TCAs continue to be superior treatments. We focused on recent findings on newer antidepressants as analgesics. Their use should be supported by further controlled trials.

Keywords: Neuropathic pain, Antidepressant, New antidepressant drugs, Antinociception, Mechanism of action, Clinical trials.

INTRODUCTION

For many years pain was considered to be the sensory response to tissue damage, without attention to the other aspects of this experience. However the relationship between affective state and pain perception is well recognized [1]. The IASP definition of pain is "an unpleasant sensory and emotional experience associated with potential or actual tissue damage or described in terms of such damage".

Fishbain reviewed psychiatric comorbidities [2] and included major psychiatry disorders (depression and panic), substance use-related disorders (alcohol and cocaine abuse), somatoform disorders and anxiety. The comorbidity between chronic pain and depression is the most common and the most exhaustively studied. Some authors reported a prevalence rate approaching 100%.

Primary depression, which can be complicated by pain, should be distinguished from secondary depression, which is caused by pain [3]. In the first case, depression is a primary major psychiatry disorder, whereas the pain can be an added problem. In the latter, as the pain increases the vulnerability to develop mood disorders, depression should be considered as the consequence of the painful syndrome, thus as secondary disorder. Depression is a virtually universal complication of intractable pain [4].

The high prevalence of comorbid pain and depression led to wide use of antidepressants in chronic pain management. Not only may they provide their primary function of mood elevation, they may also have analgesic properties.

Antidepressants have become a routine adjunctive therapy for most forms of chronic pain. Tricyclic antidepressants (TCAs) have been used for the treatment of various chronic and neuropathic pain conditions [5]. The first report on imipramine in pain management appeared 40 years ago [6], when antidepressants were introduced in clinical medicine, before their mechanisms were elucidated. Their efficacy is now well established, although the multiple mechanisms by which antidepressants produce analgesia are still unclear [7]. Their therapeutic effects in painful condition can be understood on the basis of common neurotransmitters implicated both in depression and pain. Antidepressants are thought to modulate pain perception through activity on noradrenergic and serotoninergic systems that descend from the midbrain to the dorsal horn. Despite these similarities, recent studies focused on the hypothetical different mechanisms involved in analgesia. Analgesic properties of these drugs occur independently of antidepressant action, in lower doses and with a faster onset of action.

Despite the older TCAs continue to be superior treatments for some chronic painful neuropathies, a major drawback to their use has been the high incidence of poorly tolerated side effects. Newer non-tricyclic antidepressants are emerging and their efficacy as analgesics is being studied [8].

In the United States, the Food and Drug Administration (FDA) has approved more than 20 compounds as antidepressants and the most have been tested for the treatment of chronic painful neuropathies. A classification of commercially available antidepressants is presented in Table 1.

Table 1. A Classification of Antidepressants

TRICYCLICS AND TETRACYCLICS
- Tertiary amine tricyclics
Imipramine
Amitriptyline
Clomipramine
Doxepine
Trimipramine
- Secondary amine tricyclics
Desipramine
Nortriptyline
Protriptyline
- Tetracyclics
Amoxapine
Maprotiline

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Selective Serotonin Reuptake Inhibitors (SSRIs)
Fluoxetine
Paroxetine
Sertraline
Fluvoxamine
Citalopram
Escitalopram
Monoamin Oxidase Inhibitors (MAOIs)
Phenelzine
Tranylcypromine
Isocarboxazid
Multiple Action Agents
Venlafaxine
Mirtazapine
Nefazodone
Reboxetine
Trazodone
Bupropion

ANTIDEPRESSANTS AS ANALGESICS: MECHANISMS OF ACTION

Antidepressants are complex drugs that exert multiple pharmacological actions. Recent insights into the mechanism by which antidepressants produce pain relief came from numerous studies on animal models of pain. Studies using inflammatory and nerve injury models of persistent pain have demonstrated consistent analgesic activity with antidepressants. In animals, the physiological reaction to noxious stimuli is mediated by corticoadrenal and sympathetic responses [9]. Endogenous glucocorticoid steroids inhibit prostaglandins and other inflammatory mediators, whereas the sympathetic response increases the output of neurogenic amines, norepinephrine and serotonin within the neuronal synaptic junction. Analgesic efficacy of antidepressants has been related to the ability of these drugs to inhibit these biogenic amine reuptake. This class of drugs exhibits diverse pharmacological properties and each drug has a unique profile.

Serotoninergic and noradrenergic processes are integral parts of endogenous pain inhibitory mechanisms. These neurotransmitters are involved in two "descending modulatory pathways" from the brainstem to the spinal cord, which act on the input of afferent painful signals. One pathway has predominantly the serotonin as its major neurotransmitter and originates at the level of the midbrain in the periacqueductal gray (PAG) and nucleus raphae magnus. The other originates at the level of the locus ceruleus in the medulla and it has norepinephrine as the major neurotransmitter [10].

Other receptors are involved in antidepressants mechanism of action. Histaminic, cholinergic muscarinic, and cholinergic nicotinic receptors are bound by antidepressants. However this interaction is the basis of the reported side effects.

It has been proposed that some antidepressants exert their analgesic properties through opioid-mediated mechanisms. Both Venlafaxine [11] and Mirtazapine [12], two newer antidepressants, were shown to enhance analgesia mediated by opioid receptors, when co-administrated with selective opioid agonists. Moreover, selective opioid antagonists were found to inhibit their analgesic effects. Antidepressants are thought to interact with endogenous opioid system. Chronic administration of antidepressants was shown to increase endogenous opioid levels and modify opioid receptor density.

Among other mechanisms, antidepressants were found to bind to the N-methyl-D-aspartate (NMDA) receptor complex [13] and reduce intracellular calcium concentration. [14] NMDA receptor-mediated effects in spinal nociception are involved in central sensitization and persistent neuropathic pain syndromes. The inhibition of these excitatory amino acid (EAA) receptors in the spinothalamic tract and dorsal horn was shown to decrease flinching behaviors.

Moreover antidepressants were found to inhibit the uptake of adenosine [15], which appears to be a significant mediator of analgesia [16].

Other animal studies suggested that antidepressants could activate G-coupled protein, resulting in analgesic effect. Selective antagonists of all three G proteins were shown to reduce analgesia mediated by antidepressants [17].

Finally antidepressants can inhibit ion channels. Their antidepressant activity was related to inhibition of L-type Ca^{2+} channels [18], whereas analgesic properties were related with selective N-type Ca^{2+} channel blocking [19]. Na^{+} and K^{+} channels are also involved in antidepressant-mediated analgesia.

In the past, antidepressants have been administrated, in animals, primarily by systemic routes (intraperitoneal, intravenous, oral), to mimic oral intake in humans. These studies focused on central antidepressant actions. In subsequent studies antidepressants have been administrated either into the cerebral ventricles or spinally. In general, both these routes produced analgesia, but the efficacy observed following supraspinal administration was greater than that following spinal injections [20].

Most recently peripheral administration of antidepressants received some consideration. Animal studies have shown that antidepressants may produce peripheral analgesia, though the involved mechanisms remain still unclear.

In the rat formalin test, a model of persistent pain that involves elements of both inflammation and central sensitization, Amitriptyline was shown to produce a local peripheral antinociceptive action, which is mediated, in part, by interaction with endogenous adenosine. The inhibitory effect of amitriptyline is clearly due to a local mechanism, as it was not observed following administration of Amitriptyline into the controlateral paw. The proposed

mechanism of peripheral action is the inhibition of the cellular uptake of adenosine with a consequent activation of adenosine A1-receptors on sensory nerve terminals [21].

Similarly, Amitriptyline has been demonstrated to produce a peripheral antinociceptive action in a neuropathic pain model (spinal nerve ligation).

When injected locally into the neuropathic paw, Amitriptyline 100 nmol had an immediate, statistically significant antihyperalgesic effect, which persisted for 120 min following administration. Amitriptyline was effective in alleviating thermal hyperalgesia but was ineffective against mechanical allodynia, regardless of the route of administration (intraperitoneal, intrathecal and subcutaneously). In all cases, the antihyperalgesic effect was observed without a concomitant analgesic effect on the controlateral paw [22].

Desipramine also was shown to produce peripheral analgesia when locally administrated in both an inflammatory pain test (formalin test) and a neuropathic pain test (spinal nerve ligation model), whereas Fluoxetine had a peripheral antinociceptive action only in the inflammatory pain test [23].

The mechanisms by which antidepressants produce a peripheral antinociceptive action are not entirely clear.

The well-known block of the uptake of both noradrenaline and serotonin is unlikely to account for peripheral analgesia, because both these biological amines have pain-facilitating actions on peripheral sensory nerve terminals. On the other hand, the block of histamine and acetylcholine receptors could be involved in peripheral analgesia, as these molecules can facilitate peripheral pain signaling. Opioid receptors have been found also in peripheral tissue, following an inflammatory or traumatic injury [24], such that binding to opioid receptors represents a possible mechanism involved in peripheral analgesia produced by antidepressants.

Finally, antidepressants, such as TCAs, were shown to possess local anesthetic properties. They are thought to block sodium-channels both in central and peripheral nervous system [25]. In rat sciatic nerve ligation, Amitriptyline was found to be a more potent neuronal sodium-channel blocker than the local anesthetic Bupivacaine [26]. This could explain pain relief by reducing firing frequency in ectopic sites.

In summary, antidepressants exhibit the following pharmacological actions: noradrenaline and serotonin reuptake inhibition, direct and indirect opioid receptors interaction, histamine, cholinergic and NMDA receptors antagonism, ion channel activity inhibition and adenosine

Table 2. Randomized, Double-Blind, Placebo-Controlled Trial of TCAs and SSRIs to Treat Neuropathic Chronic Pain

TCAs STUDY	**YEAR**	**DRUG**	**DOSAGE mg/day**	***Pain*, diagnosis**	**n**	**OUTCOME**
Watson *et al.*	1982	Amitriptyline	75	Postherpetic neuralgia	24	+
Max *et al.*	1988	Amitriptyline	150	Postherpetic neuralgia	34	+
Kishore-Kumar *et al.*	1990	Desipramine	167 (avg)	Postherpetic neuralgia	19	+
Kvinesdal *et al.*	1984	Imipramine	100	Diabetic neuropathy	12	+
Max *et al.*	1987	Amitriptyline	25 -150	Diabetic neuropathy	29	+
Max *et al.*	1991	Desipramine	12.5 – 150	Diabetic neuropathy	20	+
Sindrup *et al.*	1989	Imipramine	125 – 200	Diabetic neuropathy	9	+
Sindrup *et al.*	1990	Clomipramine	50 – 75	Diabetic neuropathy	19	+
Sindrup *et al.*	1990	Desipramine	50 – 200	Diabetic neuropathy	20	+
Sindrup *et al.*	1990	Imipramine	25 – 350	Diabetic neuropathy	15	+
Sindrup *et al.*	1992	Imipramine	25 - 350	Diabetic neuropathy	18	+
Panerai *et al.*	1990	Clomipramine, Nortriptyline	25 - 100	Central pain	17	+
Leijon and Boivie	1989	Clomipramine	150	Post-stroke pain	15	+
Vrethem *et al.*	1997	Amitriptyline	75	Polyneuropathy	33	+
Vrethem *et al.*	1997	Maprotiline	75	Polyneuropathy	33	+
SSRIs STUDY	**YEAR**	**DRUG**	**DOSAGE mg/day**	***Pain*, diagnosis**	**n**	**OUTCOME**
Max *et al.*	1992	Fluoxetine	40	Diabetic neuropathy	46	-
Sindrup *et al.*	1990	Paroxetine	40	Diabetic neuropathy	19	+
Sindrup *et al.*	1992	Citalopram	40	Diabetic neuropathy	18	+

Modified from Lynch ME [7]

uptake block. Their analgesic properties were observed following either systemic, or supraspinal, or spinal, or peripheral administration. These recent findings on their peripheral action raise the possibility that these drugs could be given topically and could be useful as peripherally acting analgesics. Local application of Amitriptyline by cream or gel might be a useful method of drug delivery in inflammatory [21] and neuropathic pain states [22]. Percutaneous absorption of antidepressants has been assessed in mouse models [27]. In peripheral neuropathies, topical formulations are particularly useful, because these allow the delivery of effective concentrations of drug near the site of origin of the pain and reduce the incidence of side effects. The main advantage could be to increase the local concentration of antidepressant without increasing the systemic dose and subsequently depressing the central nervous or cardiac excitability.

Capsaicin, lidocaine, non-steroidal anti-inflammatory drugs and opioids are already available as topical pain treatments. In particular, in clinical trials, lidocaine patch 5% was shown to significantly relieve all neuropathic pain qualities [28]. A possible interaction between topical analgesic drugs of proved efficacy and new antidepressants formulation could be supposed.

TRICYCLIC ANTIDEPRESSANTS

Several controlled randomized double blind studies have shown that tricyclic antidepressants (TCAs) are effective analgesics. TCAs have been considered the gold standard in the treatment of neuropathic pain, as their superiority compared either to placebo or to other available drugs has been demonstrated.

Fifteen randomized placebo-controlled trials have been conducted to analyze the analgesic effects of the TCAs in neuropathic pain. There is significant evidence that the TCAs are effective in postherpetic neuralgia [29-31], in painful diabetic neuropathy [32-38], in central pain [39], in post-stroke pain [40] and in polyneuropathy [41] (Table 2).

Various TCAs were studied. Imipramine, Amitriptyline and clomipramine caused a balanced reuptake inhibition of both serotonin and noradrenaline, while desipramine and maprotiline proved relatively selective noradrenaline reuptake inhibitors.

The analgesic effect occurs in the absence of depression or where there was no antidepressant effect, at lower doses than those used for depression. In many studies, antidepressants were dosed according to the effect and side effects.

A major problem in many clinical drug trials is the failure to predict outcome because of the small sample size. A common outcome measure such as the number-needed-to-treat (NNT) has been used to compare and combine several trials. This measure unit is used for retrospective evaluation of a drug's analgesic efficacy and shows the number of patients needed to treat to produce greater than 50% pain relief [42]. NNT was statistically defined as the inverse of the absolute risk reduction, thus as the number of patients needed to treat to prevent a single bad out-come [43].

In painful diabetic neuropathy, the most extensively studied pathological condition, NNT values for TCAs are around 2-3. This means that 2-3 patients have to be treated before one patient with > 50% pain relief is obtained. When looking into individual drug groups, the NNT value for TCAs is almost identical across different painful conditions such as postherpetic neuralgia, painful polyneuropathy and peripheral nerve injury (Table 3) [44].

Furthermore, TCAs have the lowest NNT value compared to the other utilized drugs [45].

The mean challenge in using TCAs for chronic pain management remains the high incidence of intolerable side effects. TCAs are poorly selective agents and the wide range of receptor interactions is the basis of the observed adverse events. Serotonin and norepinephrine act both centrally and peripherally, in different organs and apparatuses.

Serotonin or 5-Hydroxytryptamine (5-HT) is synthesized and deposited at the level of enterochromaffin cells and play a role in regulating gastrointestinal motility. Serotonin is also involved in haemostasis. 5-HT is taken up from blood circulation and stored into the secretory granules of platelets. At the site of vascular injury, 5-HT released from platelets results in a procoagulative state with clot formation and haemostasis. Activation of 5-HT_2A receptors enhances further platelet aggregation and promotes smooth muscle cells constriction, whereas vascular endothelial 5-HT_1 receptor binding induces release of endothelium derived relaxing factor (EDRF). Moreover serotonin stimulates vasoconstriction in splanchnic, renal, pulmonary and cerebral beds, and similarly bronchoconstriction on bronchial smooth muscle.

Finally, serotonin seems to affect different brain activities, including sleeping, learning, sensorial perception, thermoregulation, appetite, sexual behavior, hormonal secretion, and, as known, pain perception [46].

Table 3. Number Needed to Treat

Agent	Diabetic neuropathy	Postherpetic neuralgia	Peripheral nerve injury	Central pain
All antidepressants	3.0 (2.4 – 4.0)	2.3 (1.7 – 3.3)	2.5 (1.4 – 10.6)	1.7 (1.0 – 3.0)
TCAs	2.4 (2.0 – 3.0)	2.3 (1.7 – 3.3)	2.5 (1.4 – 10.6)	1.7 (1.1 – 3.0)
Imipramine, amitriptyline, clomipramine	2.0 (1.7 – 2.5)	2.4 (1.8 – 3.9)	2.5 (1.4 – 10.6)	1.7 (1.1 – 3.0)
Desipramine, Maprotiline	3.4 (2.3 – 6.6)	1.9 (1.3 – 3.7)	Not done	Not done
SSRIs	6.7 (3.4 – 435)	Not done	Not done	Not active

Adapted from Sindrup and Jensen [44]

Norepinephrine (NE) is the mean sympathetic postganglionic neurotransmitter, which binds α and β adrenergic receptors.

On the one hand, α-adrenergic receptors mediate arterial vasoconstriction, mydriasis, gut relaxation, piloerection, and bladder and intestinal sphincter contraction.

On the other hand, heart-selective β_1 receptors mediate inotropic action, resulting in increase of contractility and cardiac rate, whereas β_2 receptors cause bronchodilatation and vasodilatation. Moreover they mediate intestinal, uterine and bladder relaxation and induce thermogenesis and glycogenolysis [47].

All these functions of these two neurotransmitters are associated to various side effects. Sedation is a common side effect of TCAs, although some patients can disclaim agitation, insomnia, hallucinations and tonic-clonic seizure.

Cardiac effects should also be taken in consideration when prescribing TCAs therapy, because these represent the mean limitation to their use, especially in patients with cardiac disease, such as previous acute myocardial infarction, arrhythmias or congestive heart failure. These drugs interfere with conduction system, leading to prolonged QT intervals, rhythms abnormalities and depressed ST segments on ECGs. In healthy subjects, orthostatic hypotension has been observed, due to autonomic effects: α-adrenergic antagonism and β_2 mediated vasodilatation.

Anticholinergic effects are also common with TCAs, because of their block of cholinergic muscarinic receptors, which are located on cells activated by parasympathetic postganglionic neurons. Blurred vision, due to loss of accommodation, is a common opthalmological side effect, especially in patients affected by glaucoma. In these patients, the association of pilocarpine eyedrops is recommended, to antagonize TCAs effects. Other common anticholinergic side effects include dry mouth, constipation and urinary retention.

Noradrenaline is also involved in urinary retention and constipation, because these side effects are due respectively to α-adrenergic mediated contraction of bladder and intestinal sphincters, and β_2 mediated relaxation of bladder and intestinal muscles.

Finally, weight gain and sexual dysfunction, although not life-threatening effects, may significantly affect the quality of life and consequently reduce the compliance to therapy.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

The Selective Serotonin Reuptake Inhibitors (SSRIs) show high selectivity for 5-HT receptors and a low or null affinity with other kinds of receptors, like as α-adrenergics, muscarinics, cholinergics, histaminics [48]. These drugs act by increasing the synaptic serotoninergic availability and neurotransmission.

SSRIs were introduced in the late 1980s and their success was due to the selectivity of action.

Four major advantages have been identified in using SSRIs over other antidepressants, such as TCAs and IMAO. Firstly, the reduced incidence of side effects, due to the selective action on serotonin receptors, results in higher tolerability [49]. Secondly, pharmacokinetics properties make easier the administration: titration is not needed and drugs can be administrated once daily [50]. Thirdly, reduced interaction with other drugs has been observed, especially with sedatives, antiarrhythmics, sympathomimetics and alcohol [51]. Finally, in case of overdose these drugs show a better tolerance [52].

However, SSRIs may interact with mono-amino-oxidase inhibitors (MAOIs), causing the life-threatening central serotonin syndrome [1]. Abdominal pain, fever, diarrhea, sweating, hypertension, elevated mood, altered mental state, delirium, myoclonus, increased motor activity, irritability and hostility should be considered as warning signs of the serotonin syndrome.

Other common side effects of SSRIs include agitation, anxiety, sleep disturbance, tremor, sexual dysfunction and headache.

When studied in pain states, SSRIs have not been shown as effective as TCAs.

There are 3 controlled trials examining SSRIs in the treatment of painful diabetic neuropathy (Table 2). Max *et al.* [53] found no difference between fluoxetine and placebo. A group of 46 patients received alternatively fluoxetine (mean dose of 40 mg/day) and placebo. Only in 48 and 41 percent respectively of these patients, pain relief was effective, showing that fluoxetine is not more effective than placebo in the treatment of painful diabetic neuropathy. Other 38 patients with painful diabetic neuropathy were treated, comparing amitriptyline (mean daily dose of 105 mg) with desipramine (mean daily dose of 111 mg). 74% of amitriptyline group and 61% of desipramine group experienced pain relief, showing that desipramine has a similar analgesia to that of Amitriptyline. Moreover fluoxetine was effective only in depressed subgroup, whereas amitriptyline and desipramine were as effective in not depressed as in depressed patients.

In two smaller studies, paroxetine [54] and citalopram [55] were found to exhibiting a greater analgesic effect than placebo.

Smith analyzed twenty trials available in the literature, in a recent review [56]: between those evaluated, the positive trials were placebo-controlled. In comparative studies between SSRIs and TCAs, the analgesia obtained with TCAs was superior in every case, thus additional trials should be performed to support the use of SSRIs in analgesic treatment [57].

Furthermore, the NNT value was calculated to be 6.7 for SSRIs, compared to 2.6 for TCAs [44].

These findings show that antidepressants with both serotonin and noradrenaline reuptake inhibition have greater analgesic effects, suggesting that norepinephrine reuptake inhibition may be crucial for pain relief in diabetic and postherpetic neuralgia. Recently, it has been demonstrated that genetic elimination of norepinephrine transporters results in enhanced antinociception and that this is

attributable to increased activation of the target of noradrenaline, the α_2-adrenoreceptor. Further, morphine treatment produced greater analgesia in norepinephrine transporter knockout mice, supporting the idea that an elevation of noradrenaline by blockade of the transporter results in potentiated opioid analgesia [58].

However, a recent study was conducted, by using the formalin test in rats, in order to determine which monoamine receptor subtypes are predominantly involved in antinociceptive effects of antidepressants, by investigating antagonism of antidepressant-induced antinociception after peripheral or central administration of specific receptor antagonists. α_1-adrenoreceptors and the 5-HT_2 and 5-HT_3 receptors were shown to be involved in the antinociception induced by antidepressants, whereas the stimulation of the 5-HT_4 receptors antagonizes or buffers this analgesic effect. These results might explain why SSRIs demonstrate less antinociceptive activity than TCAs [59].

Therefore, these findings are in contrast with other studies that suggest the participation of α_2-adrenoreceptors [58,60] and 5-HT_{1A} receptors in antidepressant-induced antinociception.

MONOAMINE OXIDASE INHIBITORS (MAOIs)

Monoamine Oxidase Inhibitors are very old drugs that should be left for special situations, because of their potentially fatal toxicity. Only one study was conducted in depressed patients with atypical facial pain. Phenelzine, at dosage of 45 mg, was shown to improve both pain and depression [61].

There are no controlled trials examining the analgesic effects of MAOIs in non-depressed patients.

MULTIPLE ACTION AGENTS

Recently, newer antidepressants have been introduced in clinical use, with the mean advantage of selective action on different receptors and following significant reduction in the incidence of side effects. These new drugs have been classified, on the basis of their mechanisms of action, into three categories (Figure **1**):

- Serotonin and Noradrenegic Reuptake Inhibitors (SNaRI)
- Noradrenergic and Specific Serotoninergic Antidepressants (NaSSA)
- Noradrenaline Reuptake Inhibitors (NaRI).

The classification of newer antidepressants [62] is presented in table 4.

Table 4. A Classification of Newer Antidepressants

SNaRI	Serotonin and Noradrenergic Reuptake Inhibitors	Venlafaxine Nefazodone
NaSSA	Noradrenergic and Specific Serotoninergic Antidepressants	Mirtazapine
NaRI	Noradrenaline Reuptake Inhibitors	Reboxetine

Into multiple action agents is usually classified also bupropion, as a dopamine-norepinephrine reuptake inhibitor.

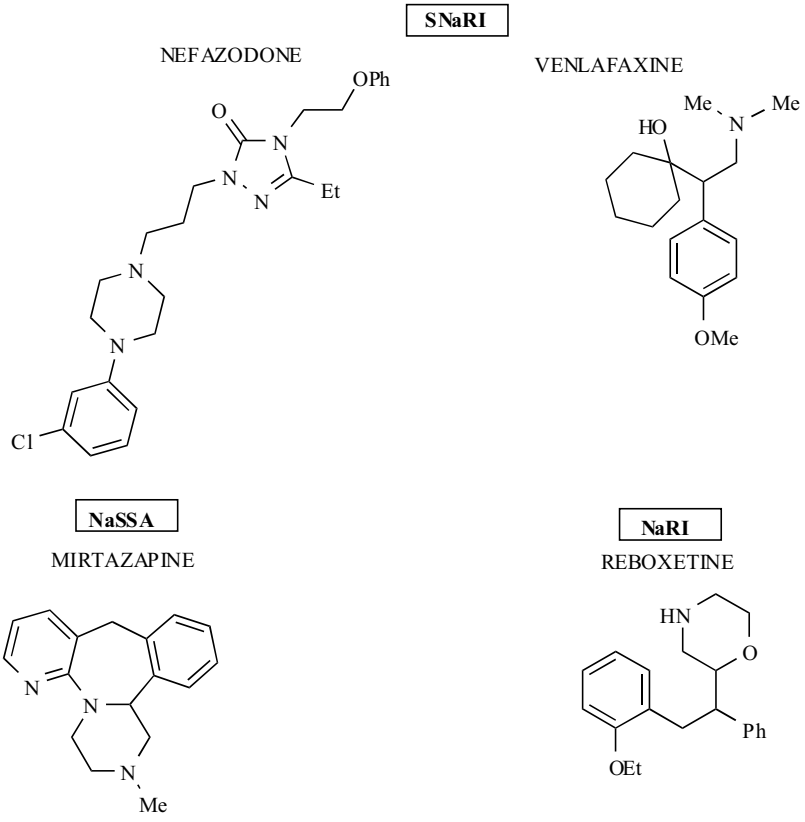

Fig. (1). Newer antidepressants.

Bupropion was first synthesized in 1966, thus is not considered into the newer antidepressants classification.

Venlafaxine

Venlafaxine (SNaRI) is a structurally novel phentylethylamine antidepressant drug. *In vitro*, Venlafaxine blocks the synaptosomal uptake of noradrenaline and serotonin. At low doses, having a very similar action to SSRIs, the serotonin reuptake inhibition predominates; however, at high doses, noradrenaline reuptake inhibition is prominent.

Moreover, venlafaxine weakly inhibits dopamine reuptake and shows *in vitro* also a low affinity for cholinergic muscarinic, H_1-histaminic and α-adrenergic receptors [63], leading to anticholinergic, sedative and cardiovascular side effects, typical of TCAs. Venlafaxine has not been shown to inhibit monoamine oxidase A or B activity.

Recently, venlafaxine was found to induce a dose-dependant opioid-mediated antinociceptive effect, when studied in the mouse hot plate assay. Velafaxine-induced antinociception was shown inhibited by naloxone, Nor-BNI and Naltrindole, implying involvement of κ_1 and δ–opioid mechanisms. Furthermore, venlafaxine was found to enhance opioid analgesia when co-administrated with selective opioid receptor agonists: DPDPE, U50488H and Nalorphine, and, to a lesser extent, Morphine. Thus, its antinociception seems to be mainly mediated by κ_1, κ_3 and δ-opioid receptors subtypes.

Moreover, Venlafaxine-antinociceptive effect is decreased by adrenergic antagonists, while it is significantly potentiated by the α_2-adrenergic agonist clonidine, implying a clear α_2– and a minor α_1–adrenergic mechanism [11].

A feasible explanation of these findings regarding opioid receptor involvement in Venlafaxine antinociception is not easy to find. Noradrenergic and dopaminergic system seem to be involved. Venlafaxine was shown to cause a down regulation of the β–noradrenergic system, which may induce an indirect activation of the opioid system supraspinally [64]. On the other hand, the Venlafaxine-induced dopamine inhibitor effect causes an increase of dopamine levels at the synaptic cleft and an antinociceptive effect that is mediated through the opioid system [65].

When administrated alone, most antidepressants were found to induce non-opioid mediated antinociception. However, when co-administrated at inactive doses with various opioids agonists, most antidepressants studied were found to enhance opioid antinociceptive effect.

Moreover, these results can explain the previous finding of a Venlafaxine-Tramadol similarity. These two agents share molecular and pharmacological features (Figure **2**). Both agents exhibit methoxyphenyl,N,N-demethylamino and hydroxycycloexyl groups; inhibit the reuptake of norepinephrine and serotonin; and are metabolized by cytochrome oxidase isoenzyme P450 2D6 and both yield pharmacologically active O-desmethyl metabolites [66]. These similarities conducted to clinical investigation about analgesic effects of venlafaxine and antidepressant augmentation effect of Tramadol. Both these drugs could be indicated in certain patient populations with comorbidity between chronic pain and depression. Although there are no published controlled trials with this agent, venlafaxine (SNaRI) is surely the most investigated of these new antidepressants in pain management. Venlafaxine is available in two formulations: immediate and extended-release. In the treatment of depression, the suggested starting dose of immediate-release venlafaxine is 75 mg/day divided into two to three doses, until a maximum dose of 375 mg/day in three divided doses. The extended-release formulation should be taken once a day, resulting in enhanced patient compliance.

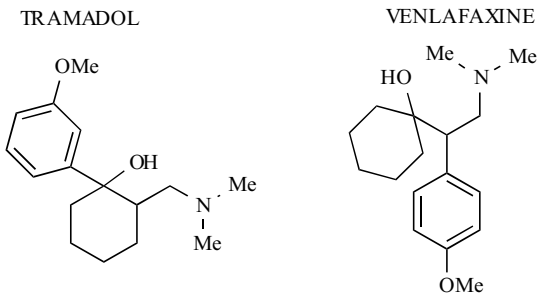

Fig. (2). Tramadol-Venlafaxine similarities.

In healthy elderly patients dose adjustment is not necessary, whereas in patients with renal failure, the dose should be reduced to 25%, and in dyalitic or hepatic insufficient patients, it should be halved.

Venlafaxine is usually well tolerated, and its side effects include nausea, dizziness, somnolence, ejaculatory abnormalities, sweating, dry mouth and nervousness. About one third of patients treated with extended-release formulation suffer from nausea. The incidence of hypertension varies from 3 to 7% at doses of 100-300 mg per day, but rises up to 13% at greater doses, thus arterial pressure monitoring is recommended [67].

The first reported case on venlafaxine as an analgesic describes a patient with radicular low back pain suffering from pain and depression. Sertraline (SSRI) was effectine in treating depression, while back pain relief was ineffective. Within three days of therapy with venlafaxine (37.5 mg twice daily), the back pain markedly decreased [68].

Taylor and Rowbotham reported a series of 12 patients affected by different peripheral neuropathies (post-herpetic neuralgia, intercostals neuralgia, atypical facial pain, multiple sclerosis). Venlafaxine was effective in pain relief, though the low number of patients involved is not enough to confirm a therapeutic success [69].

Recently, analgesic properties of venlafaxine were studied in 16 healthy volunteers, with a human experimental pain model. At doses of 37,5 mg every 12 hours, venlafaxine increased the threshold of pain tolerance by single electrical stimulation of the sural nerve. Venlafaxine efficacy in pain summation was tested, by repetitive nerve stimulations, which resulted in an increased threshold at which pain increases [70]. These results suggest a potential analgesic efficacy of venlafaxine for the treatment of chronic neuropathic pain. Similarly, rat models of neuropathy because of constriction injury of the sciatic nerve indicate a

role for venlafaxine. Rats that received Venlafaxine did not develop thermal hyperalgesia after nerve legation [71].

Different studies are available in the literature on venlafaxine efficacy in neuropathic pain treatment [72,73]. Venlafaxine has been used as a second choice drugs, when other therapies (NSAIDs, other antidepressants) have failed due either to their inefficacy or intolerable side effects. Venlafaxine was administrated at a dosage of 37.5 mg twice daily to treat chronic back pain, due to root compression. Pain relief was obtained in seven days of treatment, independently of the antidepressant effect [72]. Similarly a patient previously treated with TCAs, obtaining 50% pain relief, was switched to extended-release venlafaxine (75 mg/day), in only one administration, because of the intolerable anticholinergic side effects. Venlafaxine was shown to be as effective as TCAs in pain relieving, without side effects [73].

In the treatment of post-herpetic neuralgia, antidepressants are the drugs of choice. Venlafaxine was shown to be effective, especially when associated with Gabapentin. A possible synergy between the two drugs could be hypothesized [74, 75].

Venlafaxine was also found to be effective in the treatment of painful peripheral diabetic neuropathy. The initial dose of 75 mg/day in extended-release formulation was later increased to therapeutic dose of 225 mg/day, shared in three administrations of 75 mg [76].

Nefazodone

Nefazodone is a postsynaptic serotonin antagonist as well as a serotonin- and norepinephrine-reuptake inhibitor (SNaRI).

Nefazodone is chemically similar to Trazodone but has a more favorable side-effect profile. Trazodone has a selective serotonin reuptake inhibitory action and a selective 5-HT_2 antagonism, but its use is linked with common side effects, such as orthostatic hypotension, priapism, sedation and cardiac electrical abnormalities.

Nefazodone antagonizes the action of 5-HT_2 receptors, with a significantly weaker inhibition of NE and 5-HT reuptake than that of venlafaxine.

Postsynaptic 5-HT_2 receptor antagonism makes more serotonins to interact with other receptor subtypes, thus it increases 5-HT_1A receptor binding [77]. The mechanism of action is believed to be due to a net effect of increased neurotransmission.

Moreover, Nefazodone has the double advantage of a weak affinity for α_1 and β adrenergic receptors and no activity on histaminic, dopaminergic or muscarinic cholinergic receptors, resulting in a significantly lower incidence of side effects.

Nefazodone (SNaRI), in the treatment of depression, is used at a starting dose of 200 mg/day in two divided doses, whereas the therapeutic dose range is 300-600 mg/day. Side effects are dose-dependent, usually occurring at significantly higher doses than 300 mg/day, but a dose reduction is warranted in elderly patients, in those with liver failure and with cirrhosis.

The most common side effects associated with nefazodone are nausea, somnolence, dry mouth, constipation, asthenia and blurred vision [78]. Effects on the cardiovascular system are significantly more frequent than with placebo, consisting in systolic blood pressure reduction, asymptomatic bradycardia and prolonged QT interval. Priapism and other sexual dysfunctions have been rarely reported.

In an experimental study on rats, nefazodone was shown to have analgesic properties, especially when combined with morphine. The co-administration of morphine and nefazodone was found to enhance the analgesic effects of μ_1- and μ_2- opioid receptor related neither with increasing the lethality, nor affecting gastroenteric motility. Thus a possible analgesic rule in chronic pain treatment could be postulated [79].

Only an open-label trial has been published on analgesic efficacy of nefazodone. In patients with both diabetes mellitus as well as pain, the mean dose of 340 mg daily of nefazodone was effective in ameliorating pain, paresthesias and numbness associated with diabetic neuropathy. Furthermore, nefazodone was found to reduce HbA_{1C} levels, whereas previous studies showed that the TCAs might worsen diabetic control [80].

Further controlled trials are warranted to examine the role of nefazodone in neuropathic pain, especially in painful diabetic neuropathy.

Mirtazapine

Mirtazapine (NaSSA) has a unique pharmacological profile. The mechanism of action is via a dual enhancement of both noradrenergic and serotoninergic activity.

The noradrenergic effect is achieved through an antagonism at central pre-synaptic alpha-2-adrenergic auto-receptors, which physiologically are inhibitor receptors and prevent further noradrenaline release. Consequently, this antagonism, by blocking these auto-receptors, facilitates noradrenergic output [81]. Further, mirtazapine has been proposed to increase hippocampal serotonin levels via two interrelated mechanisms. Firstly, on the pre-synaptic side of serotoninergic neurons there are alpha-2-hetero receptors, which physiologically inhibit serotonin release. In the same manner, Mirtazapine initiates a serotonin outflow by blocking these hetero-receptors [82]. Secondly, blockade of the alpha-2-adrenergic auto-receptors, thereby facilitating adrenergic input to serotoninergic neurons of the raphae nuclei, which possess excitatory alpha-1-adrenergic receptors, increases serotonin release [83].

In addiction, Mirtazapine has a strong antagonism on 5-HT_2 and 5-HT_3 serotoninergic postsynaptic receptors, thus the net effects of serotoninergic potentiation is selectively on 5-HT_{1A} receptors [84].

Thus NaSSA differs from SNaRI because of minimum effect on amine reuptake: there is no reuptake blockade with this agent as is seen with most other antidepressants.

Venlafaxine and mirtazapine have different mechanisms of action, as they act at different sides of neuronal synapses. Venlafaxine (SNaRI) is a presynaptic drug, which blocks the

synaptosomal uptake of noradrenaline and serotonin and, to a lesser degree, of dopamine. Instead Mirtazapine (NaSSA) is a postsynaptic drug, which enhances noradrenergic and 5-HT_{1A} -mediated serotoninergic neurotransmission via antagonism of central α_2-auto- and hetero-adrenoreceptors (Figure **3**).

The selective antagonism on 5-HT_2 receptors facilitates sleep and reduces the incidence of anxiety and agitation, whereas the 5-HT_3 antagonism decreases nausea and the need for anti-emetic pharmacotherapy.

Mirtazapine has some moderate alpha-1-adrenergic antagonism that may produce an occasional orthostatic hypotension. The very low incidence of anti-cholinergic side effects has rarely produced any challenge in the patients.

The antinociceptive effect of mirtazapine has been recently studied in animal models of pain. Mirtazapine, similarly to venlafaxine, was found to induce a clear antinociceptive effect in the mouse hotplate assay. However, although venlafaxine-mediated antinociception was linear, the dose-response curve of the antinociceptive effect of mirtazapine shows a “therapeutic window effect" ; at doses from 1 to 7.5 mg/kg mirtazapine induced antinociception in a dose-dependent manner; as the dose increased beyond 10 mg/kg the analgesic effect declined, yielding a biphasic dose-response curve [85].

Mirtazapine-induced antinociceptive effect seems to be mediated through serotoninergic, noradrenergic and opioid mechanisms, as it was antagonized by the non-selective antagonist metergoline, by the alpha-2-adrenergic antagonist yoimbine and by naloxone.

The antinociceptive effect of Mirtazapine is mainly influenced by k3-opioid receptor subtype combined with both serotoninergic and noradrenergic receptors [12].

Among the antidepressants of the newer generation, the involvement of opioid system occurs only with venlafaxine and mirtazapine. Despite different mechanisms of antidepressant action, mirtazapine and venlafaxine have been shown to have common opioid-mediated antinociceptive effects. The antinociceptive effect of venlafaxine is influenced by μ, δ, κ1, and κ3 opioid receptor subtypes, whereas the antinociceptive effect of mirtazapine mainly involves μ and κ3 opioid mechanisms [85].

This new result strongly suggests a potential role of these antidepressants in pain management, but raises a question regarding a possible indirect opioid-dependence induced by mirtazapine or venlafaxine.

The withdrawal symptoms upon discontinuation of treatment with antidepressants have usually been attributed to the effects on the serotoninergic system, which may result in noradrenergic rebound or to a rebound excess of cholinergic activity, whereas opioid involvement should be looked for.

To treat depression disorders, the recommended initial dose of mirtazapine (NaSSA) is 15 mg/day, as a single dose, and the therapeutic range is between 15 and 45 mg/day. The mirtazapine has extensive hepatic metabolism culminating in glucuronide conjugation, preceded by demethylation and hydroxylation. The elimination is predominantly via the renal mechanism, accounting for about 75 percent of the dose recovered in the urine. Thus, dose reduction should be considered in the elderly and in patients with kidney (reduction of 30%) or liver (from 30 to 50%) disease. Doses below 5 mg/day are not recommended, as antihistaminergic effects predominate at lower doses, causing somnolence and sedation; whereas, with increasing doses, NE release increases, with paradoxical effect of less sedation. The most common adverse events are increased appetite and weight gain; the less common are dry mouth, constipation and dizziness. Sexual and cardiovascular side effects are absent [86].

Certain abnormalities of laboratory values have been reported, including rise in transaminases and total cholesterol, and rare cases of severe neutropenia, which developed symptomatic agranulocytosis [87]; thus a periodical blood monitoring is necessary.

Two cases of mirtazapine-induced arthralgia have been

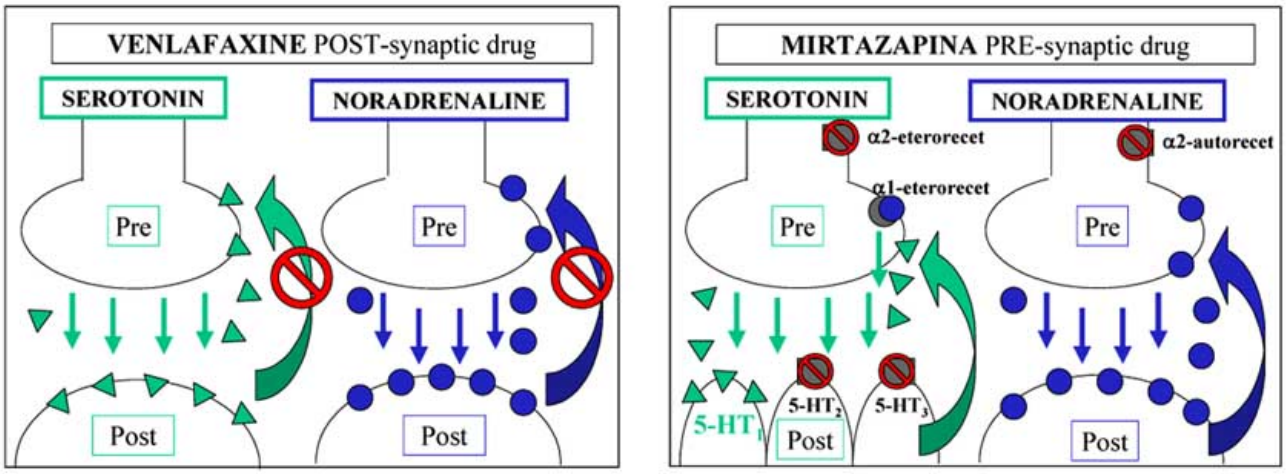

Fig. (3). Different mechanism of antidepressant action of Venlafaxine and Mirtazapine.

described. The chemical structure of mirtazapine is closely related to that of mianserin, a tetracyclic antidepressant, responsible for more than twenty cases of articular adverse effects. The mechanism of the iatrogenic arthralgia is unknown, but it is possibly the same related to their common chemical structure, as these drugs share other side effects, such as agranulocytosis [88].

The first case report on the use of Mirtazapine in a patient with chronic pain was published in 1999. After the failure of fluoxetine 20 mg/day and amitriptyline 100mg/day therapy, a patient affected from chronic back pain and depression was placed on Mirtazapine 15 mg/day at bedtime. This therapy was effective in improving his mood, in significant pain relief from 10 to 3, in a 10 VAS point scale, and in a less difficulty in walking. No sexual side effect was observed, whereas fluoxetine (SSRI) therapy has been discontinued because of low energy and sexual dysfunction [89].

Recently a pilot open-label, crossover trial of Mirtazapine in advanced cancer patients has been conducted. Despite statistically insignificant, improvement was noted at the end of the six weeks of mirtazapine therapy (crossover 15 mg/day vs 30 mg/day dose had no effects). This drug may offer cancer patients with pain a variety of benefits, including appetite, weight gain and reduction of insomnia and anxiety [90]. The analgesic effect of this antidepressant is not well clinically studied yet. Further works with mirtazapine are warranted in blinded trials and in comparison with other antidepressants with known benefits.

Reboxetine

Reboxetine has been identified as noradrenaline reuptake inhibitor (NaRI), because this drug has neither of serotoninergic, dopaminergic or monoamine oxidase inhibitory properties, but selectively inhibits norepinephrine reuptake [62].

Starting dose of reboxetine (NaRI) in treating depression is equivalent to a therapeutic dose of 8 mg/day. The dose can be increased to a maximum of 12 mg/day, if response is incomplete, whereas should be reduced to 4 mg/day as starting dose in the elderly, and as therapeutic dose in patients with renal or hepatic insufficiency [91]. Side effects, such as constipation, dry mouth and impotence, have been observed in 5% of treated men [92].

Recently, the hypothesis that a selective noradrenergic substance could be of analgesic efficacy was proven the first time experimentally. Reboxetine showed a higher analgesic potency than placebo, in capsaicin-irritated skin in healthy voluntaries, in objective tests (laser evoked somato-sensory potentials) as well as in the subjective pain measurements (visual analogue scales). Moreover, the subjective feelings of burning and itching were lower with reboxetine than with the placebo [93].

Bupropion

Bupropion was introduced soon after TCAs and emerged as an antidepressant without any anticholinergic and cardiac effects. Despite this advantage, high incidence of drug-induced seizures has been recorded, together with other side effects, such as hallucinations, dizziness and insomnia.

In late 1996, a new sustained-release formulation, bupropion SR, was approved and is now available. Bupropion SR produces neither substantial sexual side effects nor drug interactions. Moreover, seizure incidence, which concerns with high-dose IR, is substantially lower with the new SR formulation [94].

Bupropion is a dopamine-reuptake inhibitor with a weak norepinephrine and serotonin reuptake inhibition activity. Because of the noradrenaline reuptake blockade, bupropion has the potential for being analgesic antidepressants, but only a few case reports are available. These occasional reports showed positive responses in patients with low back pain at the dose of 150 mg three times daily [95]. The first open-labeled study on bupropion in neuropathic pain showed a consistent reduction of pain level after eight weeks of therapy. Twenty-two patients received 1 week of 150 mg SR bupropion once daily followed by 7 weeks of 150 mg SR bupropion twice daily. Side effects consisted primarily of insomnia, tremor, and gastrointestinal upset and had a tendency to recede with the continuation of therapy [96]. Recently, a randomized, double blind, placebo-controlled, crossover study has been conducted to evaluate the effectiveness and safety of bupropion sustained-release (SR) for the treatment of neuropathic pain. Bupropion SR at dosage of 150-300 mg daily was effective and well tolerated [97]. However this drug remains to be exhaustively studied.

CONCLUSIONS

Even though antidepressants are used routinely in pain treatment, there is not yet enough scientific evidence to recommend one antidepressant over another. There is significant evidence that the TCAs are effective analgesics, whereas SSRIs showed lower analgesic potency. The newer antidepressants could represent the future, because they are generally better tolerated than the TCAs, and their effectiveness may be increased at higher doses, without intolerable side effects [98]. However, further studies are warranted to confirm their role in chronic pain management.

On the other hand, on the basis of recent findings of experimental studies, new routes of administration for antidepressants could be supposed. Their ability in producing peripheral analgesia could be used for topical applications near the damaged peripheral nerve terminals.

Physicians should take in consideration some simple rules in prescribing antidepressant therapy for chronic pain:

1. Determinate goals of treatment
2. Select a familiar antidepressant
3. Start at low dosage and titrate upward over time
4. Inform patient about “off-label” use
5. Do not promise results
6. Switch to a different agent if current one is ineffective or has side effects

Switching from one antidepressant to the other is part of a known algorithm used at the University of Utah,

Huntsman Cancer Institute, Salt Lake City, UT, for the use of antidepressants in cancer pain. The TCAs, venlafaxine, nefazodone and mirtazapine are considered the choices. If a patient is on one of these drugs and the dose has been maximized, but pain persists, one of the other three drugs should be tried. If all these antidepressants have failed, it should be considered the opportunity for adding gabapentin [99].

Similarly, in chronic non-malignant pain the antidepressant drug should be chosen on the basis of the efficacy on the single patient and on the basis of its side effect profile.

Moreover, recent studies have shown opioid activity of some antidepressants, such as venlafaxine and mirtazapine, thus "antidepressant rotation" as well as "opioid rotation" could be considered.

ABBREVIATIONS

DPDPE	=	(D-Pen2, D-Pen5)enkephaline
EAA	=	Excitatory Amino Acid
EDRF	=	Endothelial Derived Relaxing Factor
HbA_{1C}	=	Glicosiled Hemoglobin
5-HT	=	5-Hydroxytryptamine
IR	=	Immediate release
MAOI	=	Monoamino Oxidase Inhibitors
NaSSA	=	Noradrenergic and Specific Serotoninergic Antidepressants
NaRI	=	Noradrenaline Reuptake Inhibitors
NE	=	Noradrenaline
NMDA	=	N-methyl-D-aspartate
NNT	=	Number Needed to Treat
Nor-BNI	=	Nor-binaltorphamine
PAG	=	Periacqueductal Grey
SNaRI	=	Serotonin and Noradrenegic Reuptake Inhibitors
SR	=	Slow release
SSRI	=	Selective Serotonin Reuptake Inhibitors
TCA	=	Tricyclic antidepressants
U50488H	=	Trans-3,4-dichloro-N-methyl-N-[2-(1-pyrrolindinyl)-cyclohexyl]-benzeneacetamide
VAS	=	Visual analogue scale

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