

REVIEW ARTICLE

Depression and Pain: Use of Antidepressants

Herlinda Bonilla-Jaime^{1,*}, José Armando Sánchez-Salcedo², M. Maetzi Estevez-Cabrera²,
Tania Molina-Jiménez³, José Luis Cortes-Altamirano^{4,5} and Alfonso Alfaro-Rodríguez⁴

¹Departamento de Biología de la Reproducción, Universidad Autónoma Metropolitana-Iztapalapa, Apartado Postal 55 535, C.P. 09340, Ciudad de México, México; ²Doctorado en Ciencias Biológicas y de la Salud, Universidad Autónoma Metropolitana-Iztapalapa, Apartado Postal 55 535, C.P. 09340, Ciudad de México, México; ³Facultad de Química Farmacéutica Biológica, Universidad Veracruzana, Circuito Gonzalo Aguirre Beltrán Sn, Zona Universitaria. C.P. 91090 Xalapa-Enríquez, Veracruz; ⁴División de Neurociencias, Instituto Nacional de Rehabilitación “Luis Guillermo Ibarra Ibarra”, Secretaría de Salud, Ciudad de México, México; ⁵Departamento de Quiropráctica, Universidad Estatal del Valle de Ecatepec, Ecatepec de Morelos, Estado de México, México

Abstract: Background: Emotional disorders are common comorbid affectations that exacerbate the severity and persistence of chronic pain. Specifically, depressive symptoms can lead to an excessive duration and intensity of pain. Clinical and preclinical studies have been focused on the underlying mechanisms of chronic pain and depression comorbidity and the use of antidepressants to reduce pain.

Aim: This review provides an overview of the comorbid relationship of chronic pain and depression, the clinical and pre-clinical studies performed on the neurobiological aspects of pain and depression, and the use of antidepressants as analgesics.

Methods: A systematic search of literature databases was conducted according to pre-defined criteria. The authors independently conducted a focused analysis of the full-text articles.

Results: Studies suggest that pain and depression are highly intertwined and may co-exacerbate physical and psychological symptoms. One important biochemical basis for pain and depression focuses on the serotonergic and norepinephrine system, which have been shown to play an important role in this comorbidity. Brain structures that codify pain are also involved in mood. It is evident that using serotonergic and norepinephrine antidepressants are strategies commonly employed to mitigate pain

Conclusion: Literature indicates that pain and depression impact each other and play a prominent role in the development and maintenance of other chronic symptoms. Antidepressants continue to be a major therapeutic tool for managing chronic pain. Tricyclic antidepressants (TCAs) are more effective in reducing pain than Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs).

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1. INTRODUCTION

Depression, a complex mental illness, is considered a syndrome because of the presence of numerous symptoms that can cause functional impairments or even severe disability. According to the Diagnostic Statistical Manual of Mental Disorders, fifth edition (DSM-V) of the American Psychiatric Association, depressive episodes are characterized by the presence of a depressed mood and anhedonia, the inability to

experience pleasure, for at least 2 weeks. These episodes are often accompanied by other symptoms such as a change in weight, loss of appetite, sleep disturbances, psychomotor symptoms (such as restlessness or retardation), low energy levels, feelings of low self-esteem and hopelessness, difficulty concentrating or making decisions, lack of interest in sex, and suicidal thoughts [1]. Importantly, episodes of depression may last for 6-9 months or even 2 years. Therefore, major depression is much more complex than a sensation of sadness or unhappiness; it is a mental illness and a leading cause of disability that affects 322 million people worldwide [2].

Depression is not exclusive to certain age groups, social sectors, or income levels, and its prevalence is similar in

*Address correspondence to this author at the Departamento de Biología de la Reproducción, Universidad Autónoma Metropolitana-Iztapalapa, Apartado Postal 55 535, C.P. 09340, Ciudad de México, México;
E-mail: bjh@xanum.uam.mx

high- (5.5%), low- and middle-income countries (5.9%) [3]. However, some reports have indicated that women are more susceptible to depression (5.1%) than men (3.6%) because of certain biological, psychosocial, and environmental factors [2, 4]. Although depression is more prevalent in older adulthood, it also occurs in adolescence and childhood. Commonly, the onset of depressive episodes occurs during adolescence (age: <20 years) and may extend into adulthood (age: 40 years). The risk of major depression later in life and the probability of recurrence is significantly high in individuals with a history of depressive episodes, suggesting a possible genetic predisposition [4].

As stated earlier, the etiology of depression is complex. However, depressive episodes are often triggered by stressful life events such as losing a family member or job, financial difficulties, and chronic illnesses. Although traumatic events during childhood are associated with susceptibility to develop depression in adulthood [5], not all individuals exposed to traumatic events early in life respond in the same manner to such adversities. In fact, prevalence varies widely and can be partly explained by genetic factors; for example, studies have reported that individuals with s allele of the synaptic cleft by blocking the 5-HT (SERT) gene (5-HTTLPR) are more vulnerable to depression [6].

One of the first approaches proposed to elucidate the pathophysiology of depression was the monoamine hypothesis, which posits that depression occurs because of the deficiency of monoamines (such as dopamine, norepinephrine (NE), and serotonin (5-HT)) in certain brain structures that are involved in mood regulation. This hypothesis was suggested because antidepressants increased the levels of these neurotransmitters in the SERT, norepinephrine (NET), adrenaline (NAT), and dopamine (DAT) transport by recapturing 5-HT, norepinephrine (NE), and dopamine, respectively, or inhibited the monoaminoxidase enzyme (MAO) that degrades these molecules [7]. However, low monoamine levels are insufficient to explain depression, because the onset of the therapeutic effect of these drugs is not apparent until 3-4 week of treatment [7]. In this disorder, a reduction in the hippocampal and amygdala (A) volumes is correlated with impaired learning, memory, and mood regulation [8, 9]. Significantly, all these structures are connected to the prefrontal cortex (PFC), that is, the brain circuit involved in planning, decision-making, and emotional response regulation [9]. Regarding neuronal activity in depressed patients, some reports have indicated that a reduction in the volume of the PFC and cingulate cortex (brain areas involved in emotion regulation, attention, and behavior) is observed [9]. Similarly, a decrease in the volume of the basal ganglia, thalamus, and gyrus rectus is observed in depressed patients [10]. This disruption of neuronal circuits leads to hyperactivity of the Hypothalamus-Pituitary-Adrenal (HPA) axis and the sympathetic nervous system because both the hippocampus and PFC exert negative feedback on the HPA axis, limiting its activity [11, 12]. The disruption of the HPA axis is associated with inappropriate stress responses; for example, hyperactivity increases the cortisol level, which deteriorates key neurocircuits involved in the cognitive and emotional processes [13]. Cortisol is a regulator of Brain-Derived Neu-

rotrophic factor (BDNF), which plays an important role in promoting survival, growth, differentiation, and synaptogenesis. However, an increase in glucocorticoids causes a reduction in the levels of BDNF and its receptor (TkrB) in the reduced neuronal tissue in principal brain structures involved in depression and regulation of the cognitive and emotional processes [14, 15]. These data implicate neurotrophins as participants in the alterations typical of depression and, therefore, a target for antidepressant action.

2. PAIN

The International Association for the Study of Pain defines pain as an unpleasant sensory or emotional experience associated with real or potential tissue damage or the condition described in terms of such damage. This suggests that pain is a subjective experience and that the simple presence of physical damage may or may not adequately explain pain [16]. Acute pain is a warning mechanism that prevents tissue damage; however, it may last longer than the required period of protection and persist even after the lesion has healed. Thus, acute pain can become chronic pain [17]. The World Health Organization International Classification of Diseases, eleventh revision, defines chronic pain as a persistent or recurrent condition that lasts for more than 3 months. Regardless of the etiology of chronic pain, various neuropathological mechanisms are activated in the somatosensory system. Brain imaging studies have demonstrated that various regions of the brain participate in the process of autonomous painful, affective, sensory, cognitive, motor, and inhibitory responses. This approach, the neuromatrix theory of pain, suggests that pain perception involves a nociceptive process and that chronic pain is the result of the activation of a complex neural network capable of generating rapid neuroplastic disturbances [18].

3. COMORBIDITY, DEPRESSION, AND PAIN

Emotional disorders are common comorbidities that exacerbate the severity and persistence of chronic pain, and therefore, treating patients with emotional disorders can be quite difficult [19, 20]. Specifically, depressive symptoms can intensify pain and its duration [21, 22] and may create a vicious cycle of pain and depressive symptoms. Thus, determining effective treatment for the comorbidity of depressive symptoms with pain constitutes an important challenge [23]. Currently, whether pain causes depression or whether depression amplifies pain is unclear [19, 24].

Several hypotheses have been proposed to explain this comorbidity between depression and pain. One of the hypothesis is that depression precedes the development of chronic pain or chronic pain induces depression as a symptom. The scar hypothesis states that previous episodes of depression that occurred before the onset of chronic pain predispose patients to depression once the pain sets in. Finally, it is suggested that psychological factors influence the interaction between depression and pain [25, 26]. However, although no consensus exists on a definitive hypothesis that explains the relationship between these comorbidities, evidence shows that chronic pain can trigger depressive symp-

toms and that depression can manifest as both physical and emotional pain.

Hence, the presence of chronic pain significantly increases the risk of major depression and anxiety, and vice versa. Patients with chronic pain may develop emotional problems and psychosocial disorders. Studies have reported that more than 67% of patients with chronic pain have comorbid psychiatric disorders [27], with 35% showing signs of depression and 22% manifesting neurotic disorders [28]. A study reported that 75%-80% of patients with depression experience persistent pain, especially headache, abdominal pain, neck pain, or lower back pain. In addition, studies have indicated that 20%-40% of patients with fibromyalgia have depression, whereas 17.5% of patients with persistent spinal pain have an associated mood disorder. This evidence suggests that persistent pain increases the likelihood of depression. Finally, studies have indicated that 5%-14% of patients with chronic pain attempt suicide in their lifetime, and approximately 20% have suicidal thoughts [29].

4. SENSORY PATHWAYS OF PAIN

The nociceptive perception of pain begins when specific sensory nociceptive fibers in peripheral tissues receive painful stimuli. Tissue damage-induced inflammation triggers the release of cytokines, prostaglandin E₂, histamine, and 5-HT, which increases the sensitivity of the primary sensory neurons to the stimuli (hyperalgesia). Voltage-Dependent Sodium channels (VDSCs) that play a fundamental role in the excitability of neurons in both the central nervous system (CNS) and Peripheral Nervous System (PNS) are opened upon activation by proinflammatory molecules [30]. The overexpression of these channels results in central and peripheral sensitization, similar to neuropathic pain [31]. Stimuli of this type travel along the primary afferent neuron to the dorsal horn, where they generate a synapse with the neuron that receives and projects the stimulus to the thalamus along the spinal-thalamic pathway. Finally, the stimulus is differentiated in the thalamus and projected to the somatosensory cortex, where it evokes the sensation of pain.

A peripheral lesion activates neuronal and glial cells. The ensuing neuron-glial communication influences hypersensitivity to pain [32]. Glial cells are non-neuronal cells (microglia, astrocytes, oligodendrocytes, and radial cells) that support and protect neurons in the CNS and PNS [33]. Glial cells affect the development of pain by releasing neurotransmitters such as glutamate and molecules that participate in pain pathways at the spinal and supraspinal levels. Microglia release inflammatory molecules that facilitate pain communication by coupling to their receptors on glutamatergic neurons. This bidirectional neuronal-glial interaction plays a fundamental role in the progression and persistence of pain, influencing the processing, expression, and transmission of pain [33]. Central sensitization is activated by a greater nociceptive contribution caused by lesions or inflammation, resulting in changes in the CNS. An increase in the responses of the primary afferent fibers, together with the greater spontaneous activity and excitability of the neurons in the dorsal horn and areas of the receptive field, is related to central sensitization [34, 35]. In the case of neuropathic pain, it is well known that both peripheral and spinal cord

injuries alter the expression of the neuronal sodium channel in the dorsal horn and thalamus, thus contributing to central sensitization and pain [36].

The descending pathways (inhibitors or facilitators) of the supraspinal areas join the dorsal horn. Monoaminergic (neurotransmitters: norepinephrine and serotonin) and opioidergic neurons in the descending pathways inhibit the transmission of pain. In the case of neuropathic pain, it is believed that persistence is mainly due to the activation of the descending pain-facilitating pathways and deactivation of the descending pain inhibiting pathways [16]. Glutamate is the principal neurotransmitter that activates the post-synaptic N-methyl D-aspartate (NMDA) receptors resulting in central sensitization that triggers the cascade of intracellular events, augmenting the entry of calcium ions [32]. Finally, plasticity in the CNS can trigger the central nociceptive system and produce persistent pain and hypersensitivity [37].

5. NEURAL PATHWAY BETWEEN DEPRESSION AND PAIN

Central brain structures such as the primary and secondary somatosensory, Anterior Cingulate Cortex (ACC), PFC, insular cortex, amygdala (A), thalamus (T), cerebellum, and periaqueductal gray interface are associated with the perception of pain [38]. The Ventral Tegmental Area (VTA) and nucleus accumbens (NAc) in the mesolimbic reward circuit are associated with chronic pain. The structures that regulate the emotional aspect of pain and motivational responses of an organism are the PCF, ACC, A, VTA, and NAc [38].

Interestingly, research has shown that the sensory pathways that codify pain and mood involve the same brain structures such as the insular cortex, PFC, ACC, T, hippocampus, and A [38, 39]. The projections of the amygdala converge at the amygdaloid complex, where they play a crucial role in processing stress, emotion, depression, and persistent pain [40, 41]. The amygdala contains various nuclei such as the Lateral Amygdala (LA), basolateral amygdala (BLA), and central nucleus of the amygdala (CeA), which are important for processing sensory and emotional information. In particular, the lateral capsular area of the CeA, the nociceptive amygdala, contains a large number of nociceptive neurons [42] and receives specific nociceptive information directly from the parabrachial area through the spinoparabrachial pain pathway [43]. SIRT1 protein is expressed in the CeA. The propensity of animals to develop depressive behaviors under conditions of pain has been attributed to a decrease in the expression of SIRT1 protein [41]. The CeA receives information related to affective stress [42] from the LA and BLA, which receive information related to stress and nociception from the T and cortical areas, to modulate behaviors associated with pain. The mPFC sends excitatory projections to the nucleus of the amygdala associated with the chronification of pain [44]. Chronic pain is believed to develop from the persistence of memory of pain and the inability to erase that memory after the lesion heals [45]. Neuroimaging studies have demonstrated that persistent pain is associated with morphological changes in corticolimbic regions because patients with persistent pain show reduced gray matter volume in the hippocampus and amygdala. This suggests that chronic pain is related to emotional

and cognitive changes [18]. Thus, changes in connectivity between the mPFC and NAs influence the perception of pain. Studies have shown that depression is significantly weaker in patients with chronic pain coexisting with depression. This suggests a possible modification of neuroplasticity in these patients [18]. In addition, the amygdala receives afferences from the ACC. The ACC is a brain region that combines motivational and affective information from other cerebral areas such as the T, insular cortex, and mPFC to generate one response, in this case, to pain [46-48]

The hippocampus forms part of the limbic system and regulates the Hypothalamic-Pituitary-suprarenal (HPA) axis. Therefore, the hippocampus is vulnerable to stress and depression, and changes in its volume have been reported in patients with depression [49]. Neurogenesis in the hippocampus is associated with learning and memory; however, it can also stimulate the development of chronic pain. A reduction in neurogenesis in the hippocampus is closely associated with memory deficits and aversive affective states in patients with chronic pain. However, positive regulation of neurogenesis prolongs persistent pain [50]. It is likely that neurochemical and morphological changes in the hippocampal network contribute to similar symptoms that characterize chronic pain and depression [51] because of the changes in the feedback mechanisms of the hippocampus in the HPA axis. Several reports have indicated that chronic stress exacerbates pain and the comorbidity of pain with stress-related psychiatric disorders such as depression and anxiety [52]. Studies indicate that chronic stress induces hyperactivity and a greater excitation in the BLA neurons [53], which potentiates the synaptic efficiency of the BLA-CeA pathway by activating GluN2B-NMDA receptors and sensitizing CeA neurons. This facilitates pain-related synaptic plasticity in the central parabrachial nucleus-CeA pathway, a process that has been shown to exacerbate pain in a neuropathic rat model of pain induced by nerve lesions [54].

The Dorsal Raphe Nucleus (DRN) synthesizes 5-HT. Several regions of the brain are innervated by 5-HT. Rostrally, 5-HT innervates all forebrain regions such as those that play an important role in mood, emotions, stress responses, and regulation of chronic pain in the thalamus, mPFC, insular cortex, and amygdala [55-57]. Caudally, 5-HT innervates the raphe magnus from the brainstem to the dorsal horn of the spinal cord (DHS) [58]. A high density of 5-HT_{1A} autoreceptors is located on the DRN [59], whereas the 5-HT_{1A} heteroreceptors are located on the synaptic button in the diverse regions innervated by 5-HT. 5-HT_{1A} autoreceptors and heteroreceptors bind to different types of G proteins, which appear to influence the differential signaling and desensitization of these cells. Thus, the administration of the 5-HT_{1A} agonist induces a reduction of 5-HT in the limbic brain regions and DHS [60] that modulates the release of pain neurotransmitters [61]. 5-HT_{1A} autoreceptors are targeted by antidepressants such as ISRS, which causes desensitization of 5-HT_{1A} autoreceptors more than heteroreceptors [62, 63].

Recently, Zhou *et al.* [41] demonstrated that a subpopulation of DRN serotonergic neurons (5-HTDRN) projects to the lateral habenula (LHb) through the CeA, which expresses the marker peptide somatostatin (CeASOM). 5-HT decreases

CeASOM activity through 5-HT_{1A} receptors and activates other CeA neurons through the 5-HT_{2A} receptor. They observed that in male mice with chronic pain who showed depressive behaviors, the activity of 5-HT neurons was inhibited in the DRN, and the levels of 5-HT were reduced in the CeA and increased in the peaks of CeASOM neurons.

Until recently, the effect of chronic pain on the ascending serotonergic system or the mechanism through which chronic pain modifies the central mechanisms of depression was not known. Several studies have shown that LHb is a structure that links chronic pain and depression [64]. The LHb is activated in chronic pain conditions; however, in an animal model of neuropathic pain, lesions in the LHb reduced depressive behaviors and chronic pain. Thus, the existence of a circuit that includes the LHb, DRN, and CeA raises the possibility that the reverberant activity between these structures may support depressive behaviors [65].

The existence of a circuit that includes LHb, DRN, and CeA raises the possibility that the reverberant activity between these structures can sustain depressive behavior. In this reverberant activity, a subpopulation of DRN serotonergic neurons projects toward LHb *via* CeA. Serotonergic neurons of DRN decrease CeA activity through 5HT_{1A} receptors. In turn, LHb inhibits 5-HTDRN *via* GABAergic neurons that inhibit 5-HT. In comorbid depressive and pain conditions, the disinhibition of CeASOM cells leads to the activation of glutamatergic neurons in the LHb (LHbGlu), which maintains the activity of GABAergic neurons in the DRN and further drives the LHb-DRN-CeA signaling circuit [41, 66, 67].

Evidence suggests that in addition to the involvement of 5-HT_{1A} in the DRN5HT-CeASOM pathway, 5-HT_{1A} heteroreceptors localized in the DHS and limbic regions appear to regulate pain and depression. Moreover, the administration of the 5-HT_{1A} receptor agonist (8-OH-DPAT) in the DHS inhibits the nociceptive signal in the afferent fibers of the DHS, resulting in a decrease in pain transmission [68-70]. This decrease in pain transmission is associated with a decrease in glutamate receptors in response to NMDA [71], suggesting that nociceptive signals observed are due to glutamate-dependent inhibition by the 5-HT_{1A} receptor. Furthermore, 8-OH-DPAT activates heteroreceptors in the limbic regions and exerts an antidepressant-like effect [68, 72]. In addition, these heteroreceptors located on the adjacent neurons inhibit the activity of GABA interneurons, and the glutamate input into the VTA enhances dopamine neurons to elevate mood [73].

On the contrary, the activation or overexpression of the 5-HT_{1A} autoreceptors on the DRN decreases the release of 5-HT and reduces the activity of the 5-HT_{1A} heteroreceptors on the DHS and in the limbic regions, which causes a similar behavior to depression and induces pain. Desensitization of 5-HT autoreceptors increases serotonin flux to 5-HT_{1A} heteroreceptors to produce antidepressant and antinociceptive effects [73, 74]. A strategy for the treatment of chronic pain, depression, and comorbid pain and depression [73] could be the development of drugs that preferentially activate 5-HT_{1A} autoreceptors instead of heteroreceptors or those that simultaneously block 5-HT_{1A} autoreceptors and 5-HT

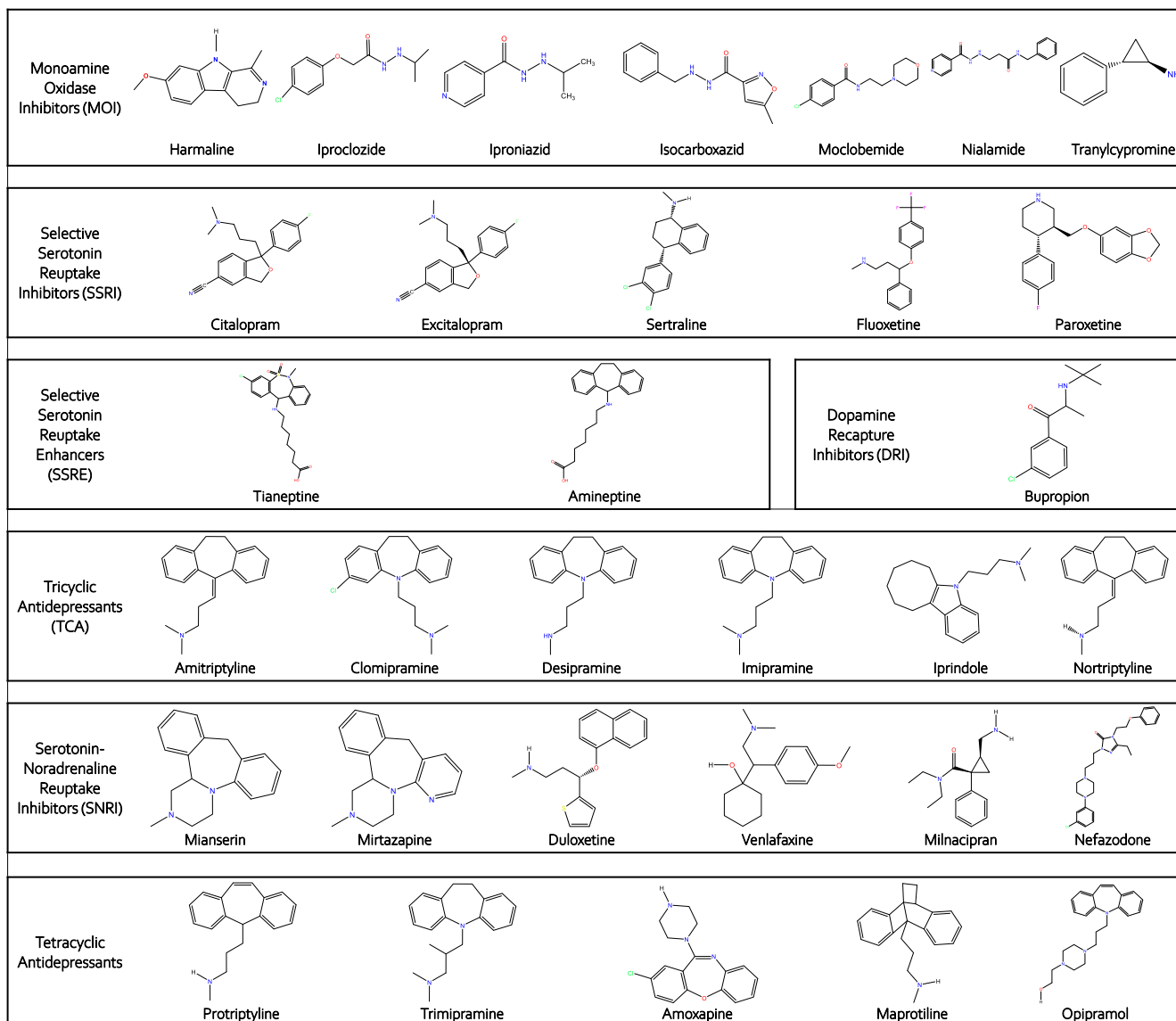


Fig. (1). Chemical structure of antidepressants: Monoamine Oxidase Inhibitors (MOI), Tricyclic Antidepressants (TCAs), Serotonin-Noradrenaline Reuptake Inhibitors (SNRI), Selective Serotonin Reuptake Inhibitors (SSRI), Selective Serotonin Reuptake Enhancers (SSRE), Dopamine Recapture Inhibitors (DRI) (<https://pubchem.ncbi.nlm.nih.gov>)

transporter to produce a more rapid onset of analgesic effects.

6. ANTIDEPRESSANTS

The classification of antidepressants is based on their chemical structure and partly on their primary *in vivo* effects (Table 1) [75]. The chemical structures of each antidepressant are shown in Fig. (1).

7. TRICYCLIC ANTIDEPRESSANTS

Currently prescribed tricyclic antidepressants (TCAs) include amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, and protriptyline. TCAs are characterized by a tricyclic chemical structure like that of phenothiazines. TCAs inhibit both norepinephrine (NE) and 5-HT

uptake, although the degree and selectivity of their inhibition of the transporter serotonergic or noradrenergic differ across the family. Clomipramine inhibits the 5-HT reuptake pump more effectively than the NE reuptake pump, whereas maprotiline and desipramine preferentially inhibit the NE reuptake pump. Nortriptyline inhibits NE and 5-HT reuptake and has a central anticholinergic effect [76-78].

8. SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Selective Serotonin Reuptake Inhibitors (SSRIs) are selective antidepressants because they inhibit only serotonin reuptake. This results in increased serotonin levels in the synaptic cleft. Currently, SSRIs are the most prescribed antidepressants. SSRIs include fluoxetine (Prozac), citalopram (Celexa), escitalopram (Lexapro), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor),

Table 1. Classification of antidepressants.

Monoamine Oxidase Inhibitors	Harmaline, Iproclozide, Iproniazid, Isocarboxazid, Moclobemide, Nialamide, Toloxatone, Tranylcypromine.
Tricyclic antidepressants	Amitriptyline, Clomipramine, Desipramine, Dothiepin, Doxepin, Imipramine, Iprindole, Lofepramine, Nortriptyline, Opipramol, Protriptyline, Trimipramine
Tetraacyclic	Amoxapine, Maprotiline, Mianserin, Mirtazapine
Selective serotonin reuptake inhibitors	Citalopram, Escitalopram, Etoperidone, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Zimelidine.
Selective serotonin reuptake enhancer	Tianeptine
Dopamine reuptake inhibitor	Amineptine, Bupropion

and duloxetine (Cymbalta). Vilazodone (Viibryd) and vortioxetine livoxtex (Brintellix) are the two recently approved serotonergic agents that inhibit serotonin reuptake and act directly against serotonin receptors as partial agonist-antagonist.

9. INHIBITOR SELECTIVE NOREPINEPHRINE RECAPTURE (ISNR)

ISNR inhibits both serotonin and NE reuptake pumps, and a profile comparable to that of TC.

10. ANTIDEPRESSANTS AND PAIN

Various antidepressants are prescribed to reduce pain independent of their mood-regulating qualities. The pain alleviation action of antidepressants involves regulation of the perception and transmission of pain. Studies have indicated that imipramine provides pain relief, an effect secondary to mood improvement, in patients with autoimmune disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis [79].

Antidepressants repress pain through several mechanisms, and therefore, they are essential drugs for the treatment of several types of persistent pain [80, 81]. Their main mechanism of action consists of increasing the inhibition of the afferent pathways to the supraspinal and spinal regions and the amounts of norepinephrine and 5-HT the synaptic button. Studies on chronic pain have reported that voltage-gated sodium channels play a key role in chronic pain because they are fundamental to the excitability of neurons in the CNS and PNS. Research has shown that antidepressants with the capacity to block the sodium channel are effective in suppressing persistent pain [82].

11. TCAS AS ANALGESICS

TCAs are the most used drugs in patients with chronic pain. NE reuptake inhibitors such as amitriptyline, imipramine, nortriptyline, and maprotiline are more effective in inhibiting pain than antidepressants without this action [80]. The analgesic mechanism of TCAs is a combination of their effects. However, these effects differ in effectiveness and their potential to cause adverse effects in patients. One mechanism is the inhibition of the serotonergic system on the spinal neural activity in the descending spinal bulb. This has been demonstrated by administering serotonin receptor antagonists that inhibit the antinociceptive effects of TCAs

[80, 81]. Importantly, the antinociceptive effects of TCAs decrease when 5-HT is exhausted at the central level upon administration of p-chlorophenyl alanine [83].

Similar to the serotonergic action of TCAs, it is believed that the analgesic effect of TCAs consists of an inhibitory influence on noradrenalin at the level of the descending spinal bulb because exhaustion of norepinephrine at the central level with α -methyl-p-tyrosine or α -adrenoreceptor antagonists inhibits the antinociceptive action of TCAs [83, 84]. The antinociceptive effect of TCAs occurs through α_2 adrenoceptors, not α_1 adrenoceptors [85]. In addition to the serotonergic and noradrenergic effects, TCAs exert effects on the opioidergic system, adenosine receptors, and sodium channels, indicating that TCAs can increase the density of receptors and the level of opioids in some brain structures [86-91]. In animal studies, the formalin test revealed that the administration of clomipramine, dothiepin, amitriptyline, and sibutramine improved the antinociceptive effect [85, 88]. However, the effect of clomipramine was blocked when naloxone was administered [85]. The administration of an inhibitor of the catabolism of acetylcholine (racecadotril) with TCAs such as dothiepin and amitriptyline improved the antinociceptive effect [88]. The antinociceptive effect of TCAs was inhibited by an adenosine receptor antagonist [80, 83].

12. SSRIS AS ANALGESICS

Unlike TCAs, SSRIs have a wide range of pharmacological actions that contribute to their analgesic effect as well as increase their propensity to cause adverse effects. Fluoxetine, citalopram, and paroxetine are used to treat headaches, migraines, and other non-neuropathic forms of chronic pain but are far less efficacious than TCAs [92]. The hot plate test revealed that fluvoxamine, paroxetine, fluoxetine, and citalopram exert an antinociceptive effect, unlike escitalopram, which failed to induce any effect. The results of the hot plate test revealed that fluvoxamine exerted a dose-dependent effect, whereas citalopram and fluoxetine had a very weak effect. The opioid antagonist naloxone did not block the antinociceptive effects of fluvoxamine, fluoxetine, and citalopram [93], unlike paroxetine. In addition, paroxetine was inhibited by the serotonin 5-HT₃ receptor antagonist (ondansetron), suggesting that the SSRI may act through the serotonergic system as well as through its interaction with the opioidergic system [94]. Although SSRIs such as fluoxetine are the most prescribed drugs in depression disorder,

they are not recommended as the first-line treatment for chronic pain. This is because SSRIs increase the risk of hemorrhages, including gastrointestinal bleeding and hemorrhagic stroke.

13. SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) such as venlafaxine and duloxetine are used to treat major depressive and generalized anxiety disorders. SNRIs have fewer adverse effects because of the lack of affinity for M1, H1, or α 1-adrenergic receptors. Duloxetine, an FDA-approved drug, is effective in treating chronic pain such as osteoarthritis, Chronic Low Back Pain (CLBP), diabetic peripheral neuropathy, neuropathy, and fibromyalgia [95]. Although venlafaxine is not an FDA-approved drug for the treatment of pain, it is efficacious in treating atypical facial pain and ameliorating painful polyneuropathies, diabetic peripheral neuropathy, and migraine [96, 97].

14. OTHER ANTIDEPRESSANTS AS ANALGESICS

Evidence for the analgesic effect of tetracyclic antidepressants is limited. Clinical studies have demonstrated the antinociceptive effects of tetracyclic antidepressants, which are less significant than those of amitriptyline [97]. In patients with postherpetic neuralgia, maprotiline exerted analgesic effects. The hot plate test and the second phase of the formalin test in the chronic nerve constriction model of neuropathic pain revealed that mirtazapine exerts antinociceptive effects [92]. Few studies have been conducted on bupropion; however, Semenchuk *et al.* [98] reported that bupropion reduced neuropathic pain only in 73% of 41 patients.

15. ANTIDEPRESSANTS AS ANALGESICS IN PATIENTS WITH CHRONIC PAIN

One of the most used pain classification methods considers underlying pathophysiological and neurobiological mechanisms:

1. Nociceptive pain because of injury or possible tissue damage.
2. Inflammatory pain caused by inflammatory processes.
3. Neuropathic pain induced by a disease or injury that affects the somatosensory system.
4. Functional pain caused by an abnormality of the nervous system (*e.g.*, fibromyalgia, which causes hypersensitivity). In the United States, costs associated with pain exceed those associated with cancer, diabetes, and heart disease combined. The management of chronic pain has lasting effects on the quality of life of patients [27].

15.1. Nociceptive Pain

Nociceptive pain is provoked by the activation of nociceptors induced by damage to non-neural tissues. It is classified by location: somatic (superficial and deep) or visceral pain. Superfluous somatic pain includes pain in the skin,

membranes, mucous membranes, and subcutaneous tissues, whereas deep somatic pain includes pain in muscles, joints, tendons, and bones. Visceral pain includes abdominal cramps and pain because of appendicitis, peptic ulcer, and cardiac ischemia. Inflammatory pain is a nociceptive pain [99, 100]. Fluoxetine is the first-line drug for the treatment of major depressive disorders, although it has an increasing number of applications. Studies have investigated the use of fluoxetine for the management of nociceptive pain.

Literature review by Barakat *et al.* (2018) [100] revealed the possible use of fluoxetine for the management of nociceptive pain, for example, fluoxetine in combination with morphine, an analgesic for treating nociceptive pain.

These reports indicate that the administration of fluoxetine alone has an intrinsic antinociceptive effect, fewer adverse effects, and no probability of respiratory failure, peptic ulcers, or drug-induced pain. Fluoxetine combined with morphine improves analgesia induced by morphine, reduces the development of tolerance to morphine analgesia, decreases the development of dependence and withdrawal syndrome, and improves opioid-induced hyperalgesia.

Preclinical studies have reported two mechanisms that may mediate the analgesic effect of fluoxetine. The first centers on opioidergic systems; however, binding test studies reveal that the affinity of fluoxetine for opioid receptors is very low. Thus, fluoxetine cannot exert a direct opioidergic effect but can indirectly increase the level of opioid peptides enkephalin and endorphin. It has been suggested that the antinociceptive effect of fluoxetine may be because 5-HT mediates the signaling of nociceptive pain through the ascending and descending pathways [101] to the limbic structures and thus, modulates the affective aspect of pain [102].

Some clinical trials have reported that fluoxetine does not affect the pain threshold, may decrease it, or may even contribute to it. One possible explanation for this discrepancy is that 5-HT, the main mediator of the mechanism of action of fluoxetine, exerts both pro- and anti-nociceptive effects. Patients with inflammatory pain who benefit from fluoxetine treatment are opioid-dependent or opioid-tolerant patients because non-steroidal anti-inflammatory drugs and corticosteroids have diverse side effects. Fluoxetine has a positive effect in patients with rheumatic pain [103].

Antidepressants are being used to control and relieve pain in adults since the 1970s; however, they are now being prescribed to younger patients experiencing insufficient analgesia in some conditions [104]. This highlights the requirement for a specialized approach to treating pediatric pain [105]. Cooper *et al.* (2017) [106] conducted a review on chronic noncancer pain in children and adolescents because of various chronic diseases using data from four studies that compared several antidepressants in 272 participants aged 6-18 years: Brown *et al.* (2016) [107], amitriptyline (10 mg/day) with gabapentin (900 mg) for 6 weeks; 2 and 3) Saps *et al.* (2009) [108] and Bahar *et al.* (2008) [109], amitriptyline (10-30 mg/day) adjusted by weight during 4 and 8 weeks; and 4) Roohafza (2014) [110], the effect of citalopram (10-20 mg/day) versus placebo (10-20 mg/day) for 4 weeks. Unfortunately, the findings of these studies neither

provided evidence that antidepressants are effective in treating chronic noncancer pain in children or adolescents, nor evidence that any specific antidepressant is more effective than another. This is disappointing because children and adolescents with chronic pain have specific requirements for analgesia and migraine and abdominal and musculoskeletal pain are the most common complaints.

Currently, children under 18 years of age are prescribed antidepressants despite the lack of evidence of their effectiveness and safety based on extrapolations from the guidelines for adults. However, these treatments may not be reliable and may compromise the safety of young patients.

Another important aspect of this challenge is that the number of older adults is increasing because of the rapid aging of the population worldwide. Hence, the rates of comorbidities and geriatric syndromes have increased, including complaints of chronic pain, a problem that substantially increases the costs of medical care and deteriorates the quality of life of older adults.

Epidemiological studies have revealed a high prevalence of chronic pain in older adults. Liberman *et al.* (2018) [111] reported that the prevalence rates of chronic pain and geriatric syndromes were 55.2% and 85.4%, respectively, and that chronic was associated with geriatric syndromes as well as limitations in daily-living activities because of deteriorated physical functioning [112]. Unlike younger adults, older adults tend to experience pain in various parts of the body because of multiple causes. The common origins of chronic geriatric pain are musculoskeletal disorders such as osteoarthritis and lower back or knee pain.

Musculoskeletal pain is usually of nociceptive origin, but older adults experience neuropathic pain and age-related changes in the processing of peripheral and central pain that reduce their functional capacity. Depression is another common condition in older adults, with a reported prevalence of major depression of 1%-4% [113]. In addition, studies have reported that the relationship between pain and depression is bidirectional; that is, patients with pain are 1.5 times more likely to develop depression and vice versa.

Common risk factors in older adults include poor vision and impaired physical functioning [114]. However, older adults with persistent pain may experience a lack of sleep and poor nutrition, the two conditions that increase the likelihood of experiencing falls and cognitive dysfunction causing distress and loss of self-esteem and self-confidence. Pharmacological treatment with antidepressants is recommended in these patients, provided the tolerability and safety of the medication are assessed and side effects (such as constipation, sedation, dizziness, and weight change) are evaluated.

Based on the American Geriatric Society guidelines, Kollhorst *et al.* (2019) [113] considered paroxetine and several tricyclic antidepressants (such as opipramol, trimipramine, amitriptyline, and doxepin) to be inappropriate for older adults because of the high risk of adverse effects such as changes in cardiac, anticholinergic, and sedative conduction, compared with SSRIs (such as citalopram, escitalopram, sertraline, and fluoxetine) and norepinephrine and

serotonin uptake inhibitors (SSNRI) such as mirtazapine, venlafaxine, and bupropion.

15.2. Inflammatory Pain

Under normal conditions, inflammation plays an important role in protecting the body from pathogens and tissue damage. Its physiological response is to promote tissue repair. However, chronic inflammation for weeks causes more damage and pain [115] than certain pathogens [116]. The release of proinflammatory mediators such as prostaglandins, cytokines, chemokines, proteases, neuropeptides, and growth factors at sites of inflammation drives hyperalgesia and increases the sensitivity of the pain-detecting peripheral neurons. The skin, joints, and intestines are particularly susceptible to the development of chronic inflammatory pain. Chronic inflammation is crucial in important diseases such as atopic dermatitis (AD), arthritis, inflammatory bowel disease (IBD), asthma, diabetes, obesity, atherosclerosis, certain types of cancer, and Alzheimer's disease [117, 118]. In this context, an association has been found between inflammatory processes and psychiatric disorders such as depression, which appears to be bidirectional.

AD is one of the most long-lasting pruritic skin diseases. In many cases, patients scratch their skin lesions, causing erosion, ulceration, bleeding, and lichenification, all of which can aggravate AD symptoms. Sleep disturbances after prolonged night scratching and psychological difficulties such as scarring and social isolation dramatically deteriorate the quality of life of patients with AD. Therefore, proper treatment of pruritus is critical for treating AD. However, this is challenging because pruritus disease is generally resistant to antihistamines and topical corticosteroids. In the case of AD, TCAs such as amitriptyline and doxepin are effective in treating pruritus. Similarly, paroxetine, fluvoxamine, and sertraline, and ISRS have antipruritic effects. Finally, mirtazapine has been proven to be effective at low doses (7.5-15 mg) in relieving pruritus [119, 120].

Rheumatoid Arthritis (RA) affects the patient's quality of life. This is because patients with RA frequently afflict pain, depression, fatigue, and rheumatoid cachexia. Commonly used treatments include pain relievers, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and antidepressants, which provide modest benefits and often cause adverse events. No conclusive evidence is available for the efficacy of tricyclic antidepressants in reducing pain in patients with RA, although tricyclic antidepressants are often used in patients experiencing insufficient sleep or with joint pain because of fibromyalgia [121].

The main inflammatory diseases that affect the gastrointestinal tract (colon, small intestine, or both) are Crohn's disease and ulcerative colitis. Symptoms include diarrhea, an urgency to defecate, abdominal pain, rectal bleeding, fatigue, and weight loss. Currently, some antidepressants such as duloxetine, fluoxetine, and tianeptine are used to treat chronic pain and are often prescribed to control functional symptoms in conditions such as Irritable Bowel Syndrome (IBS). However, few studies have reported their effect in relieving pain; therefore, no firm conclusions can be drawn regarding the efficacy and safety of antidepressants to treat IBS. Cur-

rently, it is unclear whether any of these drugs (or drug families) have differential efficacy compared with a placebo [122].

15.3. Neuropathic Pain

According to the International Association for the Study of Pain, neuropathic pain is caused by injury or disease of the somatosensory nervous system. Categories of neuropathic pain include peripheral neuropathic pain (*e.g.*, trigeminal neuralgia, painful polyneuropathy, and post-herpetic neuralgia, and pain associated with multiple sclerosis, spinal cord injury, and vascular brain events [123]. Neuropathic pain is characterized by a burning or electric sensation; however, neuropathic pain manifests as a decrease in real muscle sensation or weakness and may co-exist with symptoms of hyper- or hypo-sensitivity [124].

In the case of neuropathic pain, antidepressants reduce pain by 50%, unlike the various treatments that, on average, reduce pain by 30% [125]. Importantly, this reduction in pain is achieved with only 20%-30% of the effective dose required to attain the antidepressant effect [126, 127].

However, this raises an important question: which antidepressant is most effective against neuropathic pain? An index that compares the efficacy of medication with the clinical results is the number needed to treat (NNT). The lower the NNT, the greater the efficiency. Finnerup *et al.* [128] reported NNTs for various antidepressants in the case of painful polyneuropathy: TCAs that inhibit NE and 5-HT reuptake (amitriptyline, imipramine, and clomipramine), is 2.1; TCAs that inhibit NE reuptake (nortriptyline and desipramine), approximately 2.5; SNRIs, 5.0; and SSRIs, 6.8. These results indicated that antidepressants that inhibit NE and 5-HT reuptake are more effective in reducing pain than those that selectively inhibit the reuptake of only one neurotransmitter. NE plays the most important role in the analgesic action of antidepressants.

Other studies have demonstrated the fundamental role of voltage-dependent sodium channels due to their critical role in the excitability of neurons in the CNS and PNS. TCAs such as amitriptyline, nortriptyline, and desipramine have been marketed to treat various conditions, many of which do not involve depression. TCAs are the first-line medications for neuropathic pain, headache (migraine), gastrointestinal syndromes, fibromyalgia, pelvic pain, and insomnia, among several others [18]. Amitriptyline, an inhibitor of 5-HT and NE reuptake, is the first-line medication for treating neuropathic pain. The side effects of amitriptyline include dry mouth, constipation, urinary retention, and orthostatic hypotension [123].

In a study of patients with distal symmetric polyneuropathy, compared with a placebo, amitriptyline (25-150 mg/day) effectively relieved pain. Moreover, amitriptyline has been found to be as effective as pregabalin, gabapentin, and duloxetine. Although the precise mechanism of action of amitriptyline is unknown, it is proposed that amitriptyline mediates hyperalgesia and allodynia by antagonism of N-methyl-D-aspartate receptors [129].

Although amitriptyline has been used to treat neuropathic pain for years, a review of 17 studies by Moore 2015 [130] did not reveal any constant benefit of amitriptyline for treating neuropathic pain. However, amitriptyline is the first-line drug owing to its success in clinical practice. Urits *et al.* (2019) [131] reported that the effectiveness of amitriptyline and nortriptyline for treating peripheral neuropathy was equivalent, as they reduced pain by 23%-26%; however, nortriptyline was not as effective as amitriptyline for treating neuropathic pain. Among SNRIs, venlafaxine (150-225 mg/day) and duloxetine (60-120 mg/day) have emerged as the first choice of medications. The most common side effect of SNRIs is nausea [123]. These medications usually take 8-14 weeks to achieve their maximum effect, but determining the correct, most effective dose often requires multiple trials and monitoring [131]. Venlafaxine, the selective 5-HT, and NE reuptake inhibitor has been used for the short-term treatment of painful DSPN at a dose of 75-225 mg/day. Venlafaxine has few side effects such as drowsiness, dizziness, and mild gastrointestinal discomfort; however, monitoring cardiac activity is recommended [129]. The National Comprehensive Cancer Network recommends venlafaxine and duloxetine to treat neuropathic pain because they relieve depression and anxiety that often accompany chronic cancer pain [124].

Aiyer *et al.* (2016) [132] reviewed 13 studies on venlafaxine and reported that venlafaxine is well tolerated and markedly reduces neuropathic pain compared with placebo; however, it is not superior to alternative medications available for treating neuropathic pain. Duloxetine, a selective NE and SE reuptake inhibitor, effectively decreases motor neuropathy, cancer-related neuropathic pain (breast cancer-related pain), and chemotherapy-related pain; it reduces motor neuropathy through the recovery of the descending inhibitory noradrenergic system in the spinal cord [131]. A recommended dose of duloxetine is 60-120 mg/day [133]. The adverse effects of duloxetine include a moderate increase in fasting plasma glucose during both short- and long-term (52 weeks) treatment, a decrease in appetite, drowsiness, sweating, and an increase in blood pressure [129, 134].

Currently, five SNRIs that exert the same beneficial effect and are being used in clinical practice are venlafaxine, desvenlafaxine, duloxetine, levomilnacipran, and milnacipran [16]. Lunn *et al.* (2014) [135] concluded that doses of 60 and 120 mg of duloxetine are effective in treating peripheral diabetic neuropathy, with infrequent serious side effects such as nausea, drowsiness, dizziness, constipation, dry mouth, and decreased appetite. However, these tend to be mild and transient. Studies have proposed different administration routes of duloxetine for better effects on pain. Topical administration of duloxetine, as a peripheral analgesic, is expected to have fewer side effects because of the comparatively low systemic concentration of duloxetine. This idea is not new because steroidal anti-inflammatory medications are readily available as topical analgesics. However, the effectiveness of this therapy is limited, and therefore, placebo-controlled studies comparing other effective therapies and topical doxepin for relieving pruritus to improve the symptoms of neuropathic pain are required [136, 137].

Antidepressants have been shown to have analgesic effects in chronic rheumatic pain conditions such as fibromyalgia, where NSAIDs are largely ineffective. Moreover, the use of antidepressants to treat peripheral neuropathic pain has been reported in studies on such conditions, except pain-induced neuropathies associated with HIV, chemotherapy, spinal cord injury, and phantom limb pain, which rarely respond to these agents [136]. Finally, the analgesic action of antidepressants is strong, with predominantly noradrenergic effects.

15.4. Functional Pain

15.4.1. Parkinson Disease

Parkinson's disease (PD), a neurodegenerative disease affecting the world population, impacts the economic aspects of healthcare. PD symptoms that draw greater clinical attention are akinesia, stiffness, tremor, and non-motor symptoms. It is known that pain is one of the most frequent symptoms of the early stages of PD. Pain may persist after diagnosis and exert an impact on the quality of life of patients. In patients with PD, the etiology of pain is a matter of controversy because patients report musculoskeletal, nocturnal, orofacial, radicular, and nociceptive pain, especially in the back. To complicate matters, common comorbidities with PD include depression, diabetes mellitus, osteoporosis, and rheumatic diseases. PD usually occurs in adulthood, and therefore, age-related pain makes treatment difficult. The presence of other critical factors increases sensitivity to pain because of reduced nociception threshold, local changes in spinal excitability, and decreased descending dopaminergic inhibition [138].

Another difficulty in treating pain in patients with PD is that the existing therapeutic strategies for pain are based on palliative medicine or guidelines for other diseases such as cancer and rheumatism. Therefore, the use of analgesics, opioids, anticonvulsants, cannabinoids, and antidepressants is often insufficient to treat pain in patients with PD.

The frequency of pain increases with disease duration and in the later stages of PD, many patients are prescribed antidepressants. Few clinical studies have evaluated the effects of antidepressants in this group, and no consensus on which antidepressant is preferable exists. Duloxetine and venlafaxine are often prescribed for pain in PD, although studies have suggested that tricyclic antidepressants show better results in treating pain. However, TCAs antidepressants use in PD is risky because it affects cognition and may trigger psychosis due to their side effects. PD is a complex disorder, and existing therapeutic approaches should be adopted, combined, or modified to meet the requirements of individual patients.

15.4.2. Fibromyalgia

Fibromyalgia is a complex chronic disease characterized by generalized joint and muscle pain, fatigue, migraine, IBS, non-restorative sleep, and cognitive problems [139]. Its prevalence worldwide ranges from 0.4% to 8% of the population. It is more common in women than in men. Pathophysiology of fibromyalgia includes hyperalgesia to experimental stimuli, abnormalities in the CNS and neuroendocrine sys-

tem, changes in the brain, and neurotransmitter dysfunction. These conditions justify the use of antidepressants, especially those that regulate nociceptive responses in the CNS.

Although the main antinociceptive properties of antidepressants are because of the modulation of the 5-HT, NE, and adrenergic receptor levels, they can generate undesirable effects by acting on the muscarinic and histamine receptors, causing cardiotoxicity, gastrointestinal disorders, and sedation. Antinociceptive effects can have a dose-dependent effect. Thus, the optimal analgesic action of antidepressants to treat fibromyalgia is usually achieved at lower doses than those required to improve mood [140].

Duloxetine and milnacipran, the 5-HT and NE reuptake inhibitors, are considered good candidates for treating pain because they were found to reduce pain by 30% in 40% of patients with fibromyalgia. Pickering *et al.* (2018) [139] evaluated the effect of milnacipran (50-100 mg/day for 1 month) on the profile of pain modulation in 54 women and found no significant analgesic effect on global pain compared with a placebo. In fact, pain decreased similarly in both the groups, indicating the lack of efficacy of milnacipran.

Thus, tricyclic antidepressants have the highest analgesic efficacy, and amitriptyline (10-50 mg/day) is the first-line treatment for fibromyalgia. In fibromyalgia, depression and fatigue correlate with a decrease in dopamine level.

On the contrary, bupropion inhibits the transporter of dopamine and NE recapture, but not of neuronal serotonin recapture. In a case study by Gummersheimer *et al.* (2016) [141], bupropion reduced pain and improved mood and cognitive function. Palangio *et al.* (2002) [142] showed that sibutramine, a selective 5-HT/NE/dopamine reuptake inhibitor, reduced pain and fatigue and increased overall functioning in 30 patients with fibromyalgia from 4 weeks up to 8 months of treatment (10-20 mg/day), without tachyphylaxis or obvious adverse effects. Similarly, Davis *et al.* (2000) [143] treated nine patients with diabetic neuropathy with sibutramine (15 mg/day) who responded to treatment with 50%-100% pain reduction one week after treatment. However, sibutramine was withdrawn from the market in 2010.

In conclusion, determining appropriate treatment for fibromyalgia remains an important unmet requirement and challenge because several types of receptors, mediators, cells, and physiological changes that cause multiple events are involved in fibromyalgia, which emphasizes the requirement to prioritize effective control of adverse symptoms.

16. ANTIDEPRESSANTS AS A PAIN MANAGEMENT STRATEGY IN OTHER PATHOLOGIES

16.1. Osteoarthritis and CLBP

Osteoarthritis is a degenerative joint disease characterized by cartilage degradation, synovitis, subchondral bone sclerosis, and osteophyte formation [144]. Duloxetine is a drug used for the management of osteoarthritic pain. A study of Japanese patients with chronic knee osteoarthritis demonstrated that duloxetine (60 mg/day for 48 weeks) improved pain and the physical, mental, and emotional health of pa-

tients. Pregabalin exerts a similar effect in osteoarthritis of the hand [131].

CLBP is a very common condition that drastically affects the quality of life of patients physically, emotionally, and economically. CLBP treatment generally consists of administering NSAIDs; however, if the pain is refractory, duloxetine is recommended because duloxetine has been proven effective in treating CLBP regardless of sex, age, and the duration and intensity of pain at a dose of 60 mg/day. Depression commonly coexists in patients with CLBP, and therefore, 91.1% of the effect of antidepressants (such as duloxetine) is estimated to be analgesic, and 8.9% is estimated to be antidepressant [145].

17. GASTROINTESTINAL DISORDERS

The side effects of TCAs, especially sedation and constipation, can be used to mitigate symptoms of disorders of gut-brain interaction (DGBI), where the pain is prominent. The mechanism of action of these antidepressants and the additional antagonistic properties of the 5-HT_{2A} and 5-HT_{2C}, histamine, and muscarinic receptors, increase the likelihood of more severe side effects, making TCAs suitable for treating some DGBI disorders such as sleep disturbances and diarrhea [146].

Most studies of TCAs have been performed in patients with IBS. The positive effects on pain reduction in these studies have been observed at recommended doses (25-150 mg/day) [146]. TCAs are effective for treating pain in patients with functional dyspepsia [147]. Although no formal evidence supporting the use of SNRIs in DGBI exists, fewer side effects than TCAs have been reported; thus, SNRIs may be an option for the treatment of DGBI. The use of duloxetine (30-90 mg/day) and venlafaxine (225 mg/day) for the treatment of DGBI has been investigated; however, further research is warranted [146]. Mirtazapine, the tetracyclic antidepressant, has been found to be efficacious for treating DGBI, especially in the case of functional dyspepsia. In addition, it is important to treat postprandial distress syndrome and chronic nausea or vomiting syndrome associated with weight loss. Mirtazapine (15 mg/day) improves symptoms and induces weight gain [146].

18. ANTIDEPRESSANTS AS ANTINOCICEPTIVE DRUGS IN ANIMAL MODELS OF CHRONIC PAIN

Historically, the first animal models of depressive consequences of chronic pain failed to show comorbidity of this condition with depression. However, other studies have reported anxiety or depression-like consequences in rodent models [148]. Although comorbid pain and depression have long been recognized, their foundations are complex. Experimental studies have found that antidepressants have antinociceptive and analgesic effects, and therefore, they can be used in combination to treat chronic pain [149]. Most studies have focused on the HPA, neuroinflammatory factors, neurogenesis, glutamate, GABA, and various neurotransmitters and neuromodulators. In this regard, 5-HT, dopamine, and NE are the most intensely studied candidates in both the fields, chronic pain and depression [145, 150, 151].

Five major classes of antidepressants act by increasing the levels of one or more of these neurotransmitters [152]. The establishment of appropriate animal models has aided in the exploration of these mechanisms [145]. The most widely used animal model of chronic pain imitates common chronic pain pathologies [150]. Based on the underlying pathophysiological and neurobiological mechanisms, two types of chronic pain strongly associated with depression have been described in animal models: 1) nociceptive-chronic pain (visceral and inflammatory pain); and 2) neuropathic, fibromyalgia, or functional pain [18, 153].

18.1. Nociceptive Pain

Rodent models of pain test nociceptive based on reflex responses (*e.g.*, tail-flicking, hot or cold plate, and radiant heat paw-withdrawal) because verbal evaluations used with human patients are not applicable [153]. Behavioral responses in rodents, such as exploration, locomotor activity, rearing, and food and water consumption, may decrease during painful events and reflect an overall decrease in well-being. Grooming, freezing, eye closure, or blinking may be exacerbated during painful experiences in response to nociception [154]. In addition, activities that involve pleasure, such as the preference for a sucrose solution and engaging in social interaction, are evaluated [155].

In addition to standard pain medications, low doses of antidepressants are commonly prescribed to treat several chronic pain conditions, even when depression is not a factor. This applies especially to TCAs, whose effectiveness at low doses is higher than that of other groups of antidepressants [152].

In rodent models, the response to thermal, mechanical, and chemical stimuli are assessed based on pawing, licking, jumping, and vocalizing, which suggests the participation of supraspinal pathways. In these rodent models, SSRI (escitalopram) induced antinociception. However, other studies in mice indicated that escitalopram does not have analgesic activity at low doses but induces a weak antinociceptive effect at extremely high doses (150 and 200 mg/kg body weight) [149]. In addition, contradictory results were obtained for the effectiveness of fluoxetine in similar thermal, chemical, electrical, and inflammatory pain models [100]. In studies of chronic pain (*e.g.*, headache), only tail suspension tests showed reduced immobility after treatment with flunarizine, an antidepressant used as a prophylactic antimigraine drug [156].

Hence, the tail-flick test is distinct from other thermal pain tests (hot plate and Hargreaves tests) because the tail-flick response is a spinally mediated reflex, and thus, the tail-flick test provides rapid, reproducible results. This permits the evaluation of whether a certain compound can induce acute nociceptive stimuli that are processed at the level of the spinal cord. Amitriptyline (15 mg/kg), the tricyclic antidepressant, showed significant analgesic efficacy, manifested in a marked increase in the latency to tail-flicking compared with the control group [157]. TCAs are commonly used to treat symptoms of IBS, a common disease characterized by peripheral and central hyperalgesia [158].

Visceral pain may originate in any of the thoracic, pelvic, or abdominal organs and is often accompanied by affective complications such as anxiety and emotional distress. Visceral pain is the cardinal symptom of IBS, but stress and negative emotions markedly increase visceral pain in the absence of an observable colonic injury [158, 159]. Hence, rodent models are used to assess the pathophysiology of nociception and to develop new treatment approaches for patients with visceral pain [159].

In the abdominal constriction test, administration of diluted acetic acid produces a characteristic writhing response in mice, which is representative of peritoneovisceral inflammatory pain. In this model, amitriptyline was effective in reducing the response writhing induced by acetic acid [157]. Similarly, Vargas *et al.* (2019) [160], in a chemical model of visceral pain, found that pre-treatment of mice with clomipramine, intraperitoneally or intrathecally, significantly decreased the antinociceptive ED₅₀ of various NSAIDs such as ketoprofen, piroxicam, and paracetamol. This effect may be because of the control of nociception by diverse neuromodulators such as monoaminergic systems.

Tissue inflammation is a factor that sensitizes the nociceptive nerve ending, leading to allodynia and hyperalgesia [153]. SSRI inhibits 5-HT recapture, improves depressive behavior, reduces inflammation, and alleviates neuroinflammation, which upregulates the 5-HT level [145]. Freund's complete adjuvant (CFA)-induced arthritis model is one of the main models used to study the comorbidity of inflammatory pain and depression. CFA induces inflammation in the paw to model arthritis in the temporomandibular or tibiotarsal joint and obesity, which is another significant risk factor for developing arthritis [153]. In the CFA model, the 5-HT level is depleted; however, treatment with TCA amitriptyline increases the 5-HT level and restores pain- and depression-related behavioral responses in the CFA model. Further, fluoxetine does not affect mechanical allodynia but blocks the anxiodepressive-like consequences induced by sciatic nerve injury in the CFA model [150].

The analgesic and antidepressant effects of fluoxetine were found to be moderate in the lumbar disc herniation model because of the normalization of 5-HT concentrations and TNF- α mRNA expression, although inflammation persisted [145]. The anti-allodynic effect of fluoxetine can be enhanced by increasing spinal 5-HT_{2A} receptor responsiveness. 5-HT is involved in the antinociceptive response of 5-HT₇ receptors. The 5-HT_{1A/1B} receptors are involved in mechanical allodynia but not in thermal allodynia [161]. It has been proposed that reduction in central serotonin induces depression as well as pain because central 5-HT is involved in the nociceptive pain signaling pathway and the ascending and descending modulatory pathways [145].

18.2. Fibromyalgia and Neuropathic Pain

Although the pathogenesis of fibromyalgia is complex and controversial, recent studies have suggested the involvement of lipid mediators, autoimmunity, neuroinflammation, and small-fiber neuropathy in fibromyalgia [153]. Previous reports have indicated that stress is an important risk factor for depression and may trigger fibromyalgia. The

use of antidepressants has been reported to prevent abnormal stress-induced pain sensations [162].

Drugs such as pregabalin, duloxetine, and milnacipran are approved in the US for the treatment of fibromyalgia; however, their efficacy, safety, and compliance are unsatisfactory [163]. On the contrary, TCAs and SNRIs have been proven to be efficient in relieving pain related to musculoskeletal conditions such as fibromyalgia but have the significant disadvantage of low tolerability. SNRIs are better tolerated, and their effectiveness is comparable to that of TCAs, but SSRIs and monoamine oxidase inhibitors do not seem to be effective in treating fibromyalgia, suggesting dysregulation of both 5-HT and NE neurotransmission in this disorder [152].

The lack of consistent, effective treatments indicates the requirement to develop better therapies for treating fibromyalgia. Fibromyalgia models are most often used to address depression-like behaviors; they are based on biogenic amine depletion by reserpine administration in the musculoskeletal pain model induced by repeated intramuscular acetic acid injections, vagotomy, Intermittent Cold Stress (ICS), and stress-induced models [153, 164].

Hyperalgesia induced by reserpine administration is reversed by 5-HT agonists (lorcaserin and vabicaserin) probably through the regulation of neurotransmitter levels, although clinical extrapolation remains unexplored [165, 166]. Intramuscular injections of acidic saline produce widespread hyperalgesia that persists without the evidence of significant peripheral tissue damage or inflammation. In this model, non-selective reuptake inhibitors such as milnacipran exert an antihyperalgesic effect when combined with tramadol [167, 168].

ICS induces thermal hyperalgesia in mice. Contradictory results have been reported depending on the route of administration. Intrathecal administration of milnacipran, amitriptyline, mianserin, and paroxetine had an acute analgesic effect; however, intravenous administration of these antidepressants failed to provide relief [164]. An animal model of pain developed with vagotomy has not been studied extensively; however, both gabapentin and amitriptyline have been found effective for treating sub-diaphragmatic vagotomy-induced pain, which is somewhat similar to fibromyalgia syndrome [169].

Another type of functional pain is neuropathic pain. Neuropathic pain is the direct consequence of a lesion or disease affecting the somatosensory system. Nearly 90% of comorbidity studies of depression are based on chronic nerve compression by the ligation of several nerves [153]. Thus, Chronic Constriction Injury (CCI) is a common animal model used to study nerve compression-induced neuropathic pain and its treatment [170].

Evidence from diverse studies reveals that TCAs and SNRIs are the most effective drugs for treating various neuropathic pain conditions with and without depression comorbidity [152, 171]. On the contrary, fluoxetine cannot attenuate pain induced by compression of the sciatic nerve [161]. Murad and Ayuob (2015) [172] demonstrated that in an animal model, oral fluoxetine exerted antiallodynic effects

without altering the locomotor activity and attenuated mechanical allodynia and thermal hyperalgesia, whereas milnacipran attenuated thermal (4°C plate) and mechanical (von Frey filaments) allodynia. In addition, amitriptyline exerted antiallodynic effects, except for cold allodynia [170]. On the contrary, Hu *et al.* (2016) [173] demonstrated that SNRIs such as duloxetine significantly reversed both mechanical hypersensitivity and depression-like behavior in animals with CCI. Thus, it can be inferred that SNRIs are more efficacious in treating neuropathic pain than NRIs, although the latter are two-fold more effective than SSRIs probably because of the pronociceptive actions of serotonin on its 5-HT receptors [173].

CONCLUSION

Syndromes such as depression are considered multifactorial in etiology because symptoms vary widely. Chronic pain is characterized by the activation of several neurophysiological and somatosensory mechanisms. The nature of chronic pain makes patients more sensitive to emotional disturbances that can exacerbate the perception, intensity, and duration of nociception and may form a feedback loop (vicious cycle) that makes diagnosis and treatment difficult.

Several factors, such as age, are associated with chronic pain. Older patients tend to have a complex relationship between depression and pain, whereas 20.6% of young people with depression experience headache, stomach, or back pain. Up to 88% of patients with chronic pain have additional diagnoses, and therefore, determining a suitable therapeutic approach for these painful conditions that accompany depression is a great challenge.

Research has demonstrated that the sensory pathways of pain and mood share the same brain regions such as the insular cortex, PFC, ACC, thalamus, hippocampus, and amygdala, especially the CeA. Dysfunction of the serotonergic system has been implicated in both depression and chronic pain disorders. This dysfunction is centered in the DRN, a structure involved in both chronic pain and depression because its projections innervate several brain structures such as the thalamus, amygdala, and medial cortex, PFC, and insular cortex, all of which participate in the central regulation of chronic pain. Recently, studies have identified a new pathway involved in depression and pain, which indicates that the DRN sends projections to the SOMCeA. This connection to the lateral habenula pathway may mediate at least some aspects of CDS; however, additional research is required to determine the influence of the neurotransmitters and structures involved in CDS.

Several animal, preclinical, and clinical studies have reported that certain antidepressants exert antinociceptive and analgesic. These studies have suggested that the mechanisms involved may be mediated by various conditions and that lower doses of antidepressants may be sufficient for the management of mood changes. This review presents important evidence that TCAs are more effective in reducing pain than SSRIs and SNRIs.

Further studies in both animal and human models investigating the mechanisms of all types of antidepressants and their usefulness for relieving pain are warranted. It is unclear

whether antidepressants can prevent the development of chronic pain; however, they should be prescribed after evaluating for factors such as age, sex, and the type and duration of pain. In addition, comorbidities such as depression, heart disease, and amputations should be assessed in relation to the treatment of chronic pain with antidepressants.

We emphasize that additional research is required because numerous uses of these drugs are unexplored. Moreover, it is necessary to demonstrate that such therapies will play a central role in treating pain conditions in the future. Existing knowledge should be complemented by translation studies in animals and humans with an appropriate comparison of phenotypes to the documented reality of the comorbidity of pain with depression and the underlying complexity of this condition.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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