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Chronic Pain Pharmacological Treatment in Patients with Depressive Disorders

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Abstract

Background and Objective: Frequently patients with chronic pain show depressive disorders. The co-morbidity of pain and depressive disorders has a negative impact on the patient's outcome, with an increase of the costs relating to health expenses, a reduction of productivity and a reduction of a probable remission of depressive symptoms. Following the evidences till now examined and reported, the study group elaborated recommendations for the pain and depressive disorder treatment.

Databases and Data Treatment: We searched all potentially relevant publications in Medline database from 1990 to 2014. A quality assessment was conducted categorizing following a power of evidence criteria.

Results: Forty-six relevant publications were identified: 34 randomized and controlled studies (RCT), 11 meta-analyses or reviews of literature and 1 observational open-label.

Conclusions: In a condition of co-morbidity of chronic pain and depressive disorder there is poor evidence for the tricyclic antidepressant efficacy. Among the inhibitors of the serotonin-noradrenalin reuptake, duloxetine proved to be efficient in the short-long term treatment of the pain and depressive disorder states. There is poor evidence for the inhibitor use of serotonin re-uptake in the co-morbidity states of arthritis pain and depressive disorder, against their higher efficacy in the irritable bowel syndrome.

Introduction

Rationale

Frequently patients with chronic pain show depressive disorders. Some epidemiological studies report a prevalence rate of depressive disorders in patients with a chronic pain at about 65% [1,2]. In studies conducted in hospitals about 69% of patients with depressive disorders showed mean moderate pain, while only 38,6% of patients without depressive disorders showed this pain symptomatology. The co-morbidity of pain and depressive disorders has a negative impact on the patient's outcome: there is an increase of the costs relating to health expenses, there is a reduction of productivity with an increase of absence from working days, and a reduction of a probable remission of depressive symptoms [3]. A wide longitudinal cohort study reported that depressive disorders are predictive of future backache episodes and muscle-skeletal symptoms [4]. Another study pointed out that backache was reported with a frequency twice higher in patients with depressive disorders than in patients without any depressive disorders [5]. Numerous studies underlined the relation between depressive disorders and pain, focusing particularly on how the risk of depressive disorders increases with respect to the different aspects of pain symptomatology (seriousness, frequency, duration). Patients with multiple pain symptoms (backache, migraine, and abdominal pain, thoracic and facial pain) have a probability from 2 to 5 times higher to develop depressive disorders [6]. For example, when pain intensity increases depressive symptoms and the diagnosis of depressive disorder become more prevalent [7,8].

Common physiological mechanisms

Numerous brain regions are involved in both depressive disorders and pain perception. The most important researches were made on the insular cortex, prefrontal cortex, anterior cingulate cortex, amygdale and hippocampus. [9]. Insular cortex is frequently activated after a pain stimulus. Some studies with functional MRI (fMRI) confirmed the insula central role in the pain procession, as well as its role in the integration of sensory and cognitive components of the pain perception [10-12]. The main characteristic of the prefrontal cortex is its role in executive functions such as memory, organization and judgment. Alterations of all these functions were observed in patients with depressive disorders [13]. In patients with chronic backache a reduction of the central grey matter density in the dorsolateral prefrontal cortex was described bilaterally [14]. The activation of the prefrontal cortex was observed in pain clinical conditions and it is associated with the role of attention or of ignoring the pain stimulus. The crucial role of the prefrontal cortex in individual differences in pain perception, in pain management and in pain spatial discrimination was observed through researches of the functional magnetic resonance (fMRI) [15,16]. The anterior cingulate cortex is connected to brain structures influencing the emotional valence of thinking, automatic and visceral responses and mood control. All these functions are altered during depressive disorders [17]. The magnetic resonance of women with depressive disorders not in therapy showed a reduction of the volume of the ventral anterior cingulate cortex and of amygdale compared with healthy patients. Moreover, in healthy volunteers the activation of functional anterior cingulate cortex was demonstrated through the magnetic resonance even as a response to pain thermal and mechanical stimuli [18]. Patients with

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headache have a significant reduction of the central grey matter in the cingulate cortex compared with healthy volunteers examined through the magnetic resonance [19]. SPECT showed a reduced blood flow in the anterior cingulate cortex in patients with chronic pain [20].

Amygdale has a great importance in the formation and maintenance of memories associated with emotional events processes, which are modified during depressive disorders. Neuroimaging studies pointed out an increase of blood flow in amygdale in patients with depressive disorders [21]. Imaging studies show an activation of amygdale as a response to different pain stimuli [22]. Hippocampus gives an important feedback inhibition on the hypothalamus-hypophysis-adrenal axis [23]. There is a direct connection between hippocampus and prefrontal cortex. Hippocampus has a crucial role in mood handling and in the formation of associative and episodic memories [24]. It was shown a reduced hippocampus volume compared with controls in adult patients with depressive disorders [25-27] with a statistically significant inverse relation between the duration of untreated depressive disorders and the level of the loss of the hippocampus volume. The hippocampus activation was shown even in healthy volunteers as a response to pain stimuli [28]. Patients with fibromyalgia present a reduced dopamine presynaptic activity in great many brain regions, included hippocampus.

Neurocircuits and neurochemistry

Neurocircuits and neurochemistry are other elements of connexion between pain pathologies and depressive disorders. Both patients with depressive disorders and those with a chronic pain have a dysregulation of the hypothalamus-hypophysis-adrenal axis [29]. Brain reacts to stress and depressive disorder activating this axis. Hippocampus and amygdale are two of the numerous brain structures controlling the activity of the hypothalamus-hypophysis-adrenal axis. Hippocampus has an inhibitory influence on the hypothalamus neurones containing the corticotrophin realising factor (CRF), while amygdale has a direct excitatory influence on them. The levels of glucocorticoids in physiological conditions seem to strengthen the hippocampus inhibition of the axis. An increase of glucocorticoids, as a response to stress factors like pain and depressive disorders, could not only damage hippocampus neurones, but reduce neurogenesis. Moreover, negative feedback mechanisms between the increased levels of glucocorticoids and the hypothalamus-hypophysis-adrenal axis (HPA) could be dysregulated as a result of a prolonged stress that could cause an incorrect response to this axis. Numerous psychiatric patients, included those with depressive disorders, show excessive activations of HPA and this alteration was proved to be normalized by antidepressant treatment [30]. Chronic pain is a persistent stress factor that can interrupt the negative feedback of glucocorticoids on HPA. This gives origin to the propagation of high levels of glucocorticoids with the consequent reduction of receptors for them in brain and in periphery (Blackburn-Munro). In animal models, a central role of CRF-1 in amygdale was shown for pain sensitization and for the development of pain anxiety [31,32]. Both patients with depressive symptoms and with pain disorders often show increased levels of circulating cytokines, included IL-6, PCR, IL-1beta, TNF alpha [33]. The activation of the pathway was observed in patients with depressive disorders [34]. Cytokines have a crucial role even in pain propagation and transmission [33,35]. Patients with a complex regional painful syndrome have a pro-inflammatory cytokine profile with higher levels of mRNA for TNF-alpha and IL-2 and reduced levels of IL-4 and IL-10 compared with the control group [36]. A similar pro-inflammatory profile was noticed in patients with peripheral neuropathy [37]. Descendant serotoninergic and noradrenergic path-ways were suggested as modulators of pain perception. Serotoninergic neurones involved in descendant path- ways are those localised in the magnus rafe nucleus (RVM), while noradrenergics have origin from the locus coeruleus of dorsal lateral pontine tegmentum nuclei (DLPT) [38]. They both project along the descendant path-ways of the horn in the spinal grey column where they exert their inhibitory influence. While in physiologic conditions their inhibitory influence is mild, in moments of acute stress they can inhibit completely the perception of the pain stimulus. Moreover serotoninergic and noradrenergic neurones spread in different brain regions and are involved even in the handling of mood, movement, cognition and other numerous processes. The malfunction of these ascendant projections can contribute to the classic depressive symptoms. Therefore serotoninergic and noradrenergic neurones of the rafe nucleus and locus coeruleus, respectively, link pain and depressive symptoms, so that their dysregulation can cause or increase both [39]. The reduced expression of different neurotrophic factors was involved in the physiopathology of pain and depressive disorders. The most representative of these factors is the brain derived neurotrophic factor (BDNF), a polypeptide operating through TrkB receptor together with tyrosine-kinase. Some studies pointed out that stressed rats have a depressive-like activity and have reduced BDNF levels. Moreover, post mortem studies on patients with an antidepressant treatment demonstrated a reduced BDNF expression in hippocampus. Heterozygous subjects were proved to have a reduced hippocampus volume because of a gene mutation codifying for BDNF [40]. There is no consent if this mutation predisposes or if it does not to anxious-depressive disorders. Homozygous mice, in BDNF mutation, show increased anxious-depressive behaviours which cannot be normalized with antidepressants [41]. BDNF expression in hippocampus was proved to be reduced even in rats under a pain stimulus [42] against this reduced expression, there is an increase of BDNF expression in the spinal cord as a response to the pain stimulus [43] that seems to guide the noradrenergic sprouting resulting from nerve lesions [44]. Evidences from models of neuronal cell cultures demonstrate a possible role of BDNF in the central sensitization (Lu).

As we have already said, serotonin and noradrenalin are neurotransmitters involved in the physiopathology of both anxiety and depressive disorder, and therefore the clinical research turned its attention to these neurotransmitters as therapeutic targets. Basing on the evidences till now examined and reported, the study group elaborated some recommendations for the pain and depressive disorder treatment. There is so a lot of evidence about the association between pain conditions and depressive disorders but there's a lack of evidence on the utility and safety of antidepressant for the treatment of this kind of patient.

Objectives

The author aimed to find and answer to these questions:

•What's the role of Tricycle antidepressants (TCA) into the management of patients affected with pain conditions and depressive disorders?

•What's the role of Serotonin-noradrenalin re-uptake inhibitors (SNRI) into the management of patients affected with pain conditions and depressive disorders?

•What's the role of Selective serotonin re-uptake inhibitors (SSRI)

into the management of patients affected with pain conditions and depressive disorders?

The objectives of these recommendations are:

•Optimize pain and depressive symptom handling

• Improve patients' physical and psychological health

• Improve patients' life quality

• Minimize adverse events due to the assumption of painkiller and antidepressant drugs.

Methods

This study was conducted by a team of experts composed of the members of the AIDS Executive Council, of the Pain Management Unit of the 2nd University of Naples, by the Neurosurgical Operative Unit of the 2nd University of Naples and by the Department of Psychiatry at the University of L'Aquila. We carried out a research in Medline (PUBMED) having as keywords the sequent terms all present together (English): chronic pain, depressive disorders and antidepressants. The selected research period goes from 1990 to 2014.

All potentially relevant publications (199) were selected but 46 screened, elected and included and the results were analyzed by all the members of the research (Figure 1) finally, recommendations were elaborated and the evidence power was indicated using letters from A to D.

Category A

Randomized and controlled clinical studies (RCT) reported statistically significant differences ($p<0.01$) between a given therapeutic approach and a specific datum of clinical outcome.

Level 1: literature reports multiple randomized and controlled clinical trials, and data are supported by meta-analysis. Level 2: literature reports multiple randomized and controlled clinical trials, but there are not sufficient studies for a correct analysis in this regard. Level 3: literature reports a single randomized and controlled trial

Category B

Information from studies allows us only to deduce risk-advantage relations between the therapeutic approach and a specific clinical outcome datum. Level 1: literature reports only studies (cohort and case control). Level 2: literature reports studies not comparative with associative or descriptive statistics (for example: relative risk and correlation). Level 3: literature reports only case reports.

Category C

Literature cannot determine if there is a risk-advantage relation between a therapeutic protocol and a specific clinical outcome datum. Level 1: meta-analysis cannot find statistically significant differences in groups and clinical conditions. Level 2: there are not sufficient studies to get a meta-analysis and randomized and controlled clinical trials did not find statistically significant differences or found insubstantial data.

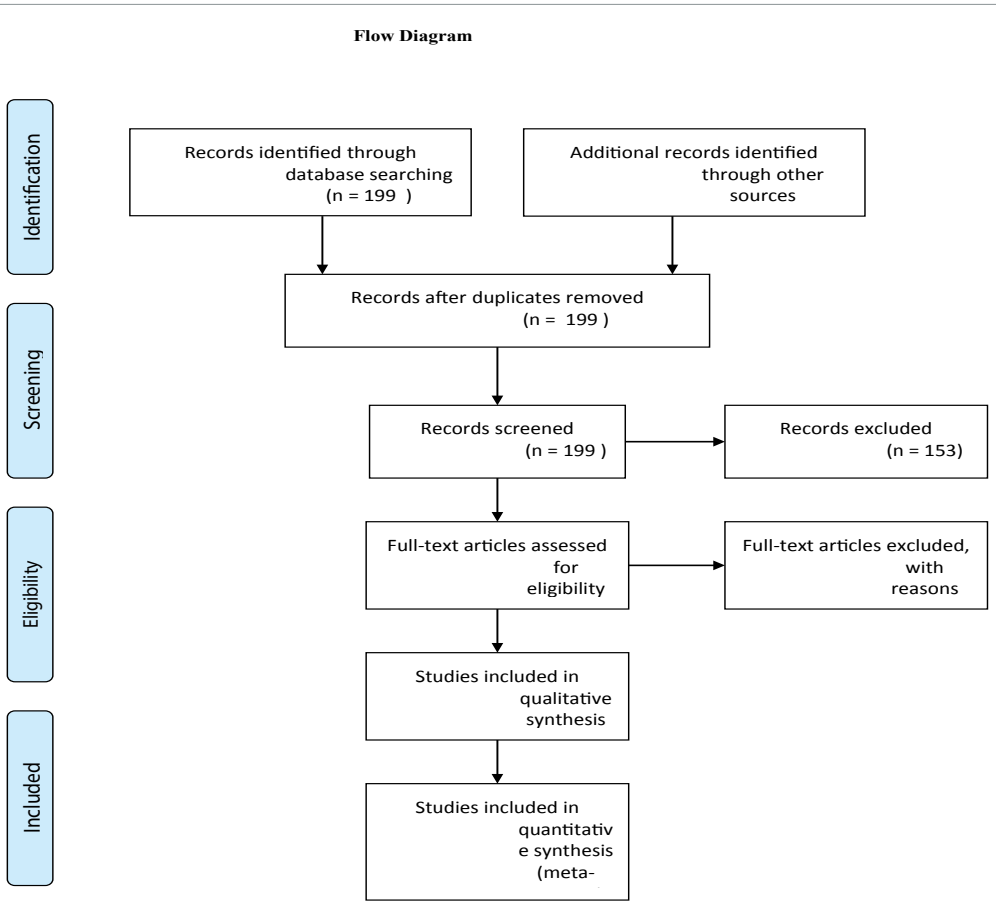

Figure 1: Flow Diagram, Chronic pain pharmacological treatment in patients with depressive disorders

Level 3: studies reported insubstantial data.

Category D

There is a lack of scientific evidence in literature as described in the following conditions: no identified study; available literature cannot be used to value risk-advantage relations for a given therapeutic protocol both because it does not fall into the inclusion criteria of guidelines and because it does not allow a clear interpretation of data.

Results

From 199 record identified through database searching, 46 relevant publications were identified because the met the eligibility criteria:

•Keywords (present all together): chronic pain, depressive disorders and antidepressants:

•Randomized controlled studies

•Meta-analyses

•Literature review

•Observational study

•Study conducted in adult patients 34 randomized and controlled studies (RCT), 11 meta-analyses or literature reviews and 1 open-label observation. The results are summarized as follows (Figure 1).

•Tricycle Antidepressants (TCA)

Tricycle antidepressants (TCA) are named like this for their organic chemical structure containing three rings. The action mechanism lies in the monoamine reuptake (noradrenalin, serotonin and/or dopamine) at synapse level (really these substances, in a prolonged treatment, show also other activities such as the modification of sensitivity and of the number of post-synaptic receptors, etc. which contribute to the antidepressant action). TCA operate, moreover, even on other neuromediators (istaminergic H1, muscarinics M1 alpha adrenergic α1, etc.) and these actions are responsible for the numerous undesired effects of these drugs: Antimuscarinics: dry mouth, urine retention, constipation, tachycardia, bleary eyes, cognitive alterations, sexual dysfunctions; Antihistamines: sedation; Antiadrenergics: orthostatic hypotension; Receptor 5-HT2c block: increase in weight. Moreover TCA can increase the risk of convulsion in predisposed subjects, cause hearth arrhythmias at a dose higher than the therapeutic ones or in predisposed subjects, transform the brachial block into ventricular-atrium block, cause acute glaucoma in subjects with closed angle glaucoma, be at toxicity risk after overdose. TCA as amitriptyline and desipramine proved to be efficient in chronic pain management such as diabetic neuropathy, fibromyalgia, headache and post-herpetic neuralgia. A meta-analysis on 39 studies was conducted with a placebo control group to evaluate the efficacy induced by antidepressants in the forms of non-cancer pain. They noticed a reduction of 74% of pain in patients treated with antidepressants compared with patients treated with placebo [45]. Their efficacy in pain management in these conditions seems independent from the antidepressant effect and rather it seems to be related directly to the serotonin-noradrenalin neuronal reuptake, and partly independent from the increased duration or concentration of these neurotransmitters in the synapses associated with the central integration of the pain stimulus. A wide literature supports the efficacy of tricycle antidepressants for the chronic pain relief [46]: post-herpetic neuralgia [47], fibromyalgia (Goldenberg), peripheral diabetic neuropathy (Jensen,), pain somatoform disorders in the orofacial region (Ikawa), chronic headache [48], and central post-stroke pain [49] (Table 1). Moore et al. [50] published a review on amitriptyline for neuropathic pain and fibromyalgia. Twenty-one studies (1437 participants). The main duration of the study examined was six weeks. Ten studies had a cross-over design. Doses of amitriptyline were generally between 25 mg and 125 mg, and dose escalation was common. There was non top-tier evidence for amitriptyline in treating neuropathic pain or fibromyalgia. Second-tier evidence indicated non evidence of effect in cancer-related neuropathic pain or HIV-related neuropathic pain, but some evidence of effect in painful diabetic neuropathy (PDN), mixed neuropathic pain and fibromyalgia. Combining the classic neuropathic pain conditions of PDN, postherpetic neuralgia (PHN) and post-stroke pain with fibromyalgia for second-tier evidence, in eight studies and 687 participants, there was a statistically significant benefit (risk ratio (RR 2.3, 95% confidence interval (CI) 1.8 to 3.1) with a number needed to treat (NNT) of 4.6 (3.6 to 6.6). The analysis showed that even using this potentially biased data, only about 38% of participants benefited with amitriptyline and 16% with placebo; most participants did not get adequate pain relief. Potential benefits of amitriptyline were supported by a lower rate of lack of efficacy withdrawals. More participants experienced at least one adverts event; 64% of participants taking amitriptyline and 40% taking placebo. The RR was 1.5. The authors concluded that amitriptyline has been a fist-line treatment for neuropathic pian for many years. The fact that there is non-supportive unbiased evidence for a beneficial effect is disappointing, but has to be balanced against decades of successful treatment in many patients with neuropathic pain or fibromyalgia. There is non-good evidence of lack of effect; rather our concern should be of over estimation of treatment effect. Amitriptyline should continue to be used as part of the treatment of neuropathic pain or fibromyalgia, but only a minority of patients will achieve satisfactory pain relief. Limited information's suggest that failure with one antidepressant does not mean failure with all. In a RCT of 8 weeks on patients with backache, made by Atkinson [51], they demonstrated the efficacy of nortriptiline at the fourth treatment week compared with the placebo treatment in reducing painful and depressive symptomatology. Another placebo controlled trial conducted by Max [52] evaluated the efficacy of desimipramine vs. placebo in patients with diabetic neuropathy in co-morbility or not with depressive disorders, pointing out a pain reduction in 13 non depressed treated patients and a reduction of painful and depressive symptoms in 7 patients with treated depressive disorders. Over the last few years Nekovarova [53] et al. has performed two pilot studies concerning the efficacy of antidepressant in patients with chronic cancer e non cancer-pain. Antidepressant (Fluoxetine and TCA) were indicated in both groups of patients for psychiatric colorability (depressions) and neuropathic pain. No of the patients had been treated with antidepressant before entering the study. The investigation started with 40 patients; 20 non-oncological patients and 20 oncological patients. The most frequent diagnosis in the non-oncological group was low back pain and failed back surgery syndrome. Therapy for both group consisted of administration of non-steroidal anti-inflammatory drugs and tramadol. As necessary, the above mentioned drugs were used in combination with: opioids, anti-epileptics, antidepressant (Fluoxetine and TCA). Although there was non difference in the intensity of pain in non-oncological patients with respect to adjuvant therapy with antidepressant, the surviving oncological patients that used antidepressant reported lower pain intensity than oncological not taking antidepressant. Despite the small number of patients, it is interesting that out of 10 patients treated with

Bibliographic Reference	N. of patients	Study design	Drug dosage	Outcome measures	Results
Atkinson et al., 1999	78	RCT	Nortriptiline 35 mg For 3 days then 5 mg for 4 days then 75 mg for 3 days then 100 mg for 4 days or placebo	DDS verbal descriptors for pain Hamilton Rating Scale for depression	Difference (95%). In media score of changes for pain intensity and for the general functional state. Depression and anxiety. No difference is reported
Max et al., 1991	24	RCT	Desipramine: dose Titration 12,5-150 mg/day,placebo	Catpi Patient Global Rating Hamilton Rating Scale for depression	Catpi : Desipramine proved to be better than placebo. Pain relief: 11/20 desipramine vs 2/2 placebo. Depression improved in desipramine group
Freynhagen et al., 2006	594	Open-label observation	Mirtazapine (daily mean dose 34,5 +/- 10,4 mg)	Patient's auto evaluation scale. Depression evaluation scale after 4 days	Pain reduction. P < 0,0001
Ambrosio et al. 2006		Review			
Tyring Sk et al. 2007		Review			
Rintala D. et al. 2007	38	RCT, Double blind cross-over	Amitriptyline, gabapentin, diphenhydramine	VAS, NRS, CESD-SF	Amitriptyline is more efficacious in relieving neuropathic pain than diphenhydramine at or below the level of spinal cord injury in people who have considerable depressive symptomatology.
Goldenberg DL et al. 2007		Review			Fibromyalgia: There is strong evidence that tricyclic antidepressants are effective, and moderate evidence for the effectiveness of serotonin reuptake inhibitors and dual serotonin-norepinephrine reuptake inhibitors. Recent work suggests that the anti-seizure medications pregabalin and gabepentin are also effective. The only analgesic demonstrated to be helpful is tramadol.
Jensen TS et al. 2006		Review			Peripheral neuropathy: An evidence-based treatment algorithm for DPNP has been proposed, recommending initial use of either a tricyclic antidepressant, selective serotonin noradrenaline re-uptake inhibitor or alpha-2-delta agonist, depending on patient co-morbidities and contra-indications.
Tomkins GE et all. 2001		meta-analysis of English-language, randomized placebo-controlled trials of antidepressants			Antidepressants are effective in preventing chronic headaches.
Frese A et al. 2006		Review			Central post-stroke pain:Amitriptyline, lamotrigine, and gabapentin provide a more favorable efficacy and safety profile than the classic antiepileptic drugs carbamazepine and phenytoin, for which no placebo-controlled evidence of efficacy was found.
Moore RA et al. 2012	1437	Review			Amitriptyline should continue to be used as part of the treatment of neuropathic pain or fibromyalgia, but only a minority of patients will achieve satisfactory pain relief.
Häuser W		Meta-analysis			The TCA amitriptyline and the SNRIs duloxetine and milnacipran are first-line options for the treatment of FMS patients. A remarkable number of patients dropout of therapy because of intolerable adverse effects or experience only a small relief of symptoms, which does not outweigh the adverse effects.

Table 1: Resuming Table-TCA, RCT: Randomized Clinical Trial; DDS: Descriptor Differential Scale; CATPI: Categorical Pain Intensity Scale.

antidepressant, survived seven, while of 10 patients not treated with antidepressant, only three patients survived. However, the authors concluded that further research with homogeneous groups was needed to establish and confirm the observed relationships. Another findings in that study was that chronic pain patients taking antidepressant had, regardless of diagnosis, higher level of gamma globulin compared to patients non treated with antidepressants. A similar observation was described by Van Hunsel et al. who found that depressed patients treated with antidepressant had a leve of gamma globulin that increased after antidepressant treatment. Only an open-label study examined TCA efficacy in treating co-morbility of pain and depressive disorders; an improvement of these symptoms was shown as a response to TCA treatment.

Hauser et al. [54] published a systematic review on the role of antidepressant in the management of fibromyalgia syndrome. Standardised mean differences (SDM) were calculated for continuous outcome by mend and standard deviations and relative risks (RR) of 30% pain reduction and total dropout rate for comparison of antidepressants with placebo. They used Cohen's categories to evaluate the magnitude of the effect size, calculated by SMD. Hauser Hueseyin et al. found 21 RCT with TCAs of which 10 with 11 study arms met ht inclusion criteria for qualitative and quantitative analyses. 717 patients we included. The SMDs to TCAs on pain, sleep, fatigue and health-related quality of life (HRQOL) were significant. Based on Cohen's categories, the effect sizes on pain and sleep were moderate and the ones on fatigue and HRQOL were small. 140/290 (48.3%) patients with TCAs and 70/252 (27.8%) patients with placebo reported a 30% pain reduction. The RR of dropouts due to adverse events was 0.84%. The use of TCA in the painful syndrome treatment was limited by the high frequency of adverse events, compared with other antidepressants and by the potential lethality after an accidental or intentional overdose [55,56].

Serotonin-Noradrenalin re-uptake inhibitors (SNRI): Serotonin-noradrenalin re-uptake inhibitors (SNRI) operate through the noradrenalin reuptake block and 5-HT at the level of prejunctional nerve endings that causes an increase of the concentration of the two amines in the synaptic space and, therefore, a higher availability for specific receptors. SRNI showed a better efficacy compared with monoamine oxidase inhibitors (MAOIs) in giving analgesia, with the analgesic effect preceding the antidepressant one. In the systematic Review on the role of antidepressant in the management of fibromyalgia syndrome conducted by Hauser W [54] thirty-five studies were included in the meta-analysis. The SMDs of serotonin noradrenaline repute inhibitors (SNRIs) on pain, sleep, fatigue, depression and HRQOL were significant. Based on Cohen's categories the effect size on pain was small and ones on sleep, fatigue, depression and HRQOL were not substantial. 1481/3528 (42.0%) patients with SNRIs and 737/2304 (32.0%) patients with placebo reported a 30% pain reduction. The RR of dropout due to adverse events was 1.83 (Table 2). In other review published on Cochrane Database Systematic Review in 2013 [57] was inseminated the role of serotonin and noradrenaline inhibitors reuptake inhibitors (SNRIs) for fibromyalgia syndrome. Ten studies were included with a total of 6038 participating. Five studies investigated duloxetine against placebo, and five investigated milnacipram against placebo. A total of 3611 participants were included into duloxetine or milnacipram groups and 2427 participants into placebo groups. The studies had a low risk of bias in general. Duloxetine and milnacipram had a small incremental effect over placebo in reducing pain (standardised mean difference (SMD) -0.23; 95% confidence interval (CI) -0.29 to -0.18; 6.1% relative improvement). One-hundred and ninety-two participants per 1000 on placebo reported an at least 50% pain reduction compared to 280 per 1000 on SNRIs (Risk ratio (RR) 1.49, 95% CI 1.35 to 1.64; number needed to treat to benefit (NNTB) 11, 95% CI 9 to 15). Duloxetine and milnacipram did not reduce fatigue substantially (SMD -0.14; 95% CI -0.19 to -0.08; 2.5% relative improvement; NNTB 17, 95% CI 12 to 29), and did not improve QOL substantially (SMD -0.20; 95% CI -0.25 to -0.14; 4.6% relative improvement; NNTB 12, 95% CI 9 to 17) compared to placebo. There were no statistically significant differences between either duloxetine or milnacipram and placebo in reducing sleep problems (SMD -0.07; 95% CI -0.16 to 0.03; 2.5% relative improvement). One-hundred and seven participants per 1000 on placebo dropped out due to adverse events compared to 196 per 1000 on SNRIs. The dropout rate due to adverse events in the duloxetine and milnacipram groups was statistically significantly higher than in placebo groups (RR 1.83, 95% CI 1.53 to 2.18; number needed to treat to harm (NNTH) 11, 95% CI 9 to 13). There was no statistically significant difference in serious adverse events between either duloxetine or milnacipram and placebo (RR 0.78, 95% CI 0.55 to 1.12).

The authors concluded that the SNRIs duloxetine and milnacipram provided a small incremental benefit over placebo in reducing pain. The superiority of duloxetine and milnacipram over placebo in reducing fatigue and limitations of QOL was not substantial. Duloxetine and milnacipram were not superior to placebo in reducing sleep problems. The dropout rates due to adverse events were higher for duloxetine and milnacipram than for placebo. The most frequently reported symptoms leading to stopping medication were nausea, dry mouth, constipation, headache, somnolence/dizziness and insomnia. Rare complications of both drugs may include suicidality, liver damage, abnormal bleeding, elevated blood pressure and urinary hesitation. In a review published by Pergolizzi et al. [58] on Duloxetine for management of diabetic, peripheral neuropathic pain, fibromyalgia and chromic musculoskeletal pain the studies reviewed reported that duloxetine 60 mg once-daily dosing is an effective option for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain due to chronic osteoarticolar pain a chronic low back pain. As these pain are often comorbid with major depressive disorders or generalized anxiety disorders, duloxetine might possess the pharmacologic properties to be a versatile agent able to address several symptoms in these patients. Numerous randomized and controlled clinical trials evaluated SNRI efficacy in the treatment of pain and depressive disorder. Chappell et al. [59] evaluated in a RCT of 13 weeks 231 patients with osteoarthritis in treatment with duloxetine from 30-120 mg. All patients presented a reduction of pain and depressive symptomatology, evaluated through Hospital Anxiety and Depression Scale (HADS). Another RCT of 9 weeks, conducted by Fava et al. on 512 patients with depressive disorders and osteoarticolar pain pointed out the efficacy of duloxetine 60 mg vs. placebo [60]. Two RCT conducted by Detke and al. on 245 patients treated with duloxetine 60 mg in 2002, and later on 367 patients treated with duloxetine or paroxetine, demonstrated an improvement in both depressive and pain symptomatology, through the score reduction in the evaluation scale of depressive and pain symptomatology [61,62]. In an RCT conducted by Perahia et al. on 392 patients, the analgesic and antidepressant efficacy of duloxetine 80-120 mg was evaluated in both acute and long term phase compared with paroxetine 20 mg [63]. Similar results were obtained by Goldstein et al. [61,62,64,65] who in three RCT on 353, 245, and 267 patients showed a higher antidepressant and antalgic efficacy of duloxetine 80 mg compared with duloxetine 40 and paroxetine 20, and then a higher antidepressant and antalgic efficacy of duloxetine 60 mg in a single administration compared with placebo. Numerous clinical studies suggest that SRNI have a direct analgesic effect independently from their antidepressant effect [66,67] both in patients with higher depressive and somatoform disorders [68] and in patients with trigeminal neuralgia. Moreover, SNRI seem to have a mean efficacy even in the atypical facial pain treatment [69]. Two randomized double blind studies, with a placebo group demonstrated the efficacy of duloxetine in the fibromyalgia treatment [70] and it was the first antidepressant drug to obtain the FDA approval in the USA for these indications.326 patients were treated with duloxetine 60 mg in a single and in a double daily administration vs 212 patients treated with placebo. Duloxetine proved to be able to improve, in a statistically significant way, the two principal parameters of efficacy, Brief Pain Inventory (BPI) and Fibromyalgia Impact Questionnaire

Bibliographic Reference	N. of patients	Study design	Drug dosage	Outcome measures	Results
Häuser W et al. 2012		Meta-analysis		pain, sleep, fatigue, depression and HRQOL	The TCA amitriptyline and the SNRIs duloxetine and milnacipran are first-line options for the patients. A remarkable number of patients dropout of therapy because of intolerable adverse effects or a small relief of symptoms, which does not outweigh the adverse effects.
Häuser W et al. 2013	6038	Review		Pain, fatigue, sleep quality, QOL	Fibrimyalgia: The SNRIs duloxetine and milnacipran provided a small incremental benefit over placebo in reducing pain. The superiority of duloxetine and milnacipran over placebo in reducing fatigue and limitations of QOL was not substantial. Duloxetine and milnacipran were not superior to placebo in reducing sleep problems.
Pergolizzi JV et al. 2013		Review	Duloxetine 60mg /die		The studies reviewed report that duloxetine 60 mg once-daily dosing is an effective option for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain due to chronic OA pain and chronic LBP. As these pains are often comorbid with MDD or GAD, duloxetine might possess the pharmacologic properties to be a versatile agent able to address several symptoms in these patients.
Chappel et al., 2009	231	RCT	Duloxetina (60-120 mg/die) Placebo	Likert Scale PGI-I; BPI-S and BPI-I; BDI-II; HADS-A. WOMAC physical functioning subscale.	A statistically significant reduction in average pain. Average variations in score BDI-II and HADS were very small
Fava et al., 2004	512	RCT	Duloxetina (60 mg/ die) Placebo	HAMD-17; CGI-S; PGI-I. VAS	Significant total pain improvement.50% of total pain improvement was independent from HAMD-17. Starting from an improvement of depression, the improvement in total pain severity was associated to higher probabilities of improvement
Detke et al., 2002	245	RCT	Duloxetina 60 mg Placebo	HAMD-17; CGI-S; PGI-I. VAS	Duloxetine was significantly better than placebo (p<0,001) in reducing HAMD-17 Duloxetine reduced significantly physical pain symptoms compared with placebo
Detke et al., 2004	367	RCT	Placebo Duloxetina 80 mg/ die (40mg BID) Duloxetina 120 mg/ die (60mg BID) Paroxetina (20 mg QD)	HAMD-17; MADRS; HAMA; VAS; CGI-S; PGI-I	Patients assuming duloxetina 80 mg/day,orparoxetine 20 mg QD vs placebo showed significantly higher reductions in the total score HADM-17. Both groups treated with duloxetine (80 and 120 mg/day) and with paroxetine showed an improvement compared with the group treated with placeboevaluated with the scales MADRS, HAMA, CGI-S and PGI-I
Perahaia et al., 2006	392	RCT	Duloxetina 80 mg/ die (40 mg BID) Duloxetina 120 mg/ die (60 mg BID) Paroxetina (20 mg QD)	HAMD-17; MADRS; HAMA; VAS; CGI-S; PGI-I	Patients treated with duloxetine 80 and 120 mg/die showed a marked improvement in HADM-17 at 8 weeks The group treated with paroxetine did not show any improvement compared with the group treated with placebo at 8 weeks. No treatment proved to be better than placebo during visits before the 8th week. Duloxetine 80 mg/day showed a significant improvement compared with placebo in the evaluation rating of scale VAS.
Goldstein et al., 2002	173	RCT	Duloxetina (40-120 mg) Fluoxetina 20 mg Placebo	HAMD-17; MADRS; VAS; CGI-S; PGI-I	Duloxetine was better than placebo in change on the HADM-17 Duloxetine was numerically better than fluoxetine in the primary evaluation and in most secondary evaluation
Goldstein et al., 2002	267	RCT	Duloxetina 60 mg/ die/die Placebo	HAMD-17; VAS; CGI-S; PGI-I; QLDS	Duloxetine (60 mg QD) reduced significantly the total score HADM-17 compared with placebo. Duloxetine reduced even the total pain. PGI-I and QLDS were significantly improved by duloxetine
Goldstein et al., 2002	245	RCT	Duloxetina 60 mg/ die/die Placebo	HAMD-17; VAS; CGI-S; PGI-I; QLDS	Duloxetine was significantly better than placebo (p<0,001) in reducing the total score HAM-D-17 Duloxetine reduces significantly painful physical symptoms compared wwith placebo
Russel et al., 2008	520	RCT	Duloxetina 20 mg/ die Duloxetina 60 mg/ die Duloxetina 120 mg/die Placebo	PGI-I; BPI; HAMD-17; FIQ	Patients treated with duloxetine 60 mg/day and duloxetine 120 mg/day show a significant improvement in pain gravity compared with placebo Path analysis shows the analgesic effect of duloxetine 60 mg/day in reducing pain severity mean score
Arnold et al., 2004	207	RCT	Duloxetina 60 mg BID Placebo	FIQ; CGI-I; BPI; PGI-I; Beck Depression Inventory.II Beck Anxiety Inventory	The group duloxetine shows a significantly higer improvement in FIQ total score. Most measures of secondary outcome improved significantly in duloxetine group vs placebo group

Arnold et al., 2005	354	RCT	Duloxetina 60 mg/die Duloxetina 60 mg BID Placebo	FIQ; CGI-I; BPI; PGI-I; HAMD-17	Duloxetine 60 mg QD and duloxetine 60 mgBID show a significantly wider improvement in BPI. There are no statistically significant differences in the comparison between duloxetine 60 mg QD and duloxetine 60 mg BID . Duloxetine 60 mg QD is statistically better in all the measures of secondary efficacy.
Geandreau et al., 2005	125	RCT	Milnacipram BID Milnacipran/die Placebo	VAS FIQ	The primary endpoint was the reduction of pain. Both group assuming the drug once/day and the group assuming it twice/day show a significant improvement in pain intensity.Improvement in general health, fatigue and other aspects.
Vitton et al., 2004	125	RCT	Milnacipran Placebo	VAS; PGIC; SF-36 FIQ; MASQ	75% of patients treated with milnacipran show an improvement compared with 38% of the group with placebo. 37% of patients treated with milnacipran twice/day show a reduction of 50% of pain intensity vs 14% of placebo group.
Clauw et al., 2008	1196	RCT	Milnacipran 100 mg/die Milnacipran 200 mg/die Placebo	VAS; PGIC; SF-36 FIQ; MASQ	Milnacipran is associated to a significant improvement of pain,significant improvement in secondary end points, included global status.
Sayar et al., 2003	15	Clinical Trial	Venlafaxina 75 mg/die	VAS; FIQ; Beck Depression Inventory-II	There is a significant improvement in mean pain intensity. Even the scores of anxiety and depression decreased significantly from the basal line. Variations in pain intensity are not correlated with variations in depression and anxiety.

Table 2: Resuming Table-SNRI.

(FIQ) from the first week of treatment to the end of the study (12 weeks). Moreover, duloxetine proved to be better than placebo in the evaluation of life quality and functional outcomes. This efficacy was confirmed by a 6 month RCT which moreover pointed out the long lasting efficacy of this treatment. The examined dosages were 60 mg/day and 120 mg/day. The dosage 60 mg/day proved to have the best profile of tolerability. Another SNRI which proved to be efficient in the fibromyalgia treatment is milnacipram. It is officially approved for the depressive disorder treatment in European and Asiatic Countries, but at the moment it is not yet on the market in Italy. The potential efficacy of milnacipram in fibromyalgia treatment was reported in two RCT flexible dose studies of 12 weeks [71,72] and in three fixed dose studies of 15 weeks [73] six months [74] and one year. In these studies, milnacipram proved to be efficient in the treatment of pain and fibromyalgia functional symptoms. Daily doses of 100 mg and of 200 mg proved to be equally efficient, with a greater tolerability of the dose 100 mg. There are fewer data supporting the efficacy of venlafaxine in fibromyalgia treatment. In a small randomized and controlled clinical study (90 patients) the efficacy of venlafaxine at the dose of 75 mg/day was evaluated with inconclusive results [75]. On the contrary another randomized clinical trial of 12 weeks pointed out that the treatment with venlafaxine is associated to a significant improvement of pain and disability compared with placebo, but the small number of patients limits its scientific value [76].

Selective serotonin re-uptake inhibitors (SSRI): The acronym SSRI means a class of substances included in the selective inhibitors of serotonin reuptake. They are called selective because, in contrast to other antidepressants, they operate exclusively on this neurotransmitter. SSRI action mechanism involves the protein that binds serotonin in the synaptic space and that takes it to the reabsorption sites at cerebral level. SSRI bind to the protein facilitating serotonin permanence in the inter-synaptic space and, consequently, facilitating the serotoninergic transmission. SSRI do not modify the total concentration of serotonin in brain. Numerous authors suggest that even other mechanisms are involved in the activity of these drugs, as the neuroprotection, immunomodulation and anti-inflammatory action, particularly through the regulation of interferon gamma, of TNF alpha and of some interleukins (IL-6, IL-10). These mechanisms could be connected to recent studies that have pointed out the role of somatic disorders (autoimmune) and of pro-inflammatory cytokines in bipolar depressive disorders. Consequently, the future of these drugs could have this specific target. SSRI generally are used in some psychiatric pathology, in depressive disorders and often even in the chronic pain. Generally their efficacy is accompanied by a prolonged long-term treatment, they do not give addiction and so they can be used even in maintenance therapies. The most common side effects are: loss of appetite, nausea, insomnia, and sexual disorders. Their assumption is not recommended in pregnancy and during breastfeeding, but when it is absolutely necessary sertraline is preferred to other molecules. When the drug is suspended symptoms like vertigo and asthenia can appear. They simulate a worsening of the psychiatric disease, but they are mild and, generally, self-limiting. Contemporary administration of tramadol and meperidine increases the risk of serotoninergic syndrome. The six main molecules belonging to SSRI drug category are: fluoxetine, sertraline, citalopram, escitalopram, fluvoxamine and paroxetine. The outcome of chronic pain with SSRI is still in phase of evaluation; in fact these drugs, with exclusively serotoninergic activity, seem not to be efficient in the improvement of chronic pain (Table 3).

In the systematic Review on the role of antidepressant in the management of fibromyalgia syndrome conducted by Hauser W [77] the authors found 14 RCTs with SSRIs of which seven met the inclusion criteria for qualitative and quantitative analyses (two studies each with citalopram and paroxetine and three studies with fluoxetine). The effect size of SSRIs on pain, sleep, depression and HRQOL were significant. Based on Cohen's categories, the effect size on pain, depression and HRQOL were small and the one on sleep not substantial. 72/198 (36.4%) patients with SSRIs and 40/194 (20.6%) patients with placebo reported a 30% pain reduction. The RR of dropouts due to adverse events was 1.60 (95% CI 0.84, 3.04; I2=0%).

A Cochrane review on neuropathic pain, where the depressive disorder was evaluated in 18 studies, 12 of which were not able to prove any effect of antidepressant drugs on it, reported a lack of activity on the facial pain. An important datum underlined the independence of pain symptom from the depressive one, in the sense that drugs had an independent analgesic action, a datum obtained comparing the scales related to pain with the ones connected to depressive disorders [78]. Although the evidence of their efficacy in the irritable bowel syndrome (IBS) is poor, a recent trial shows an improvement of the systemic symptomatology given to a specific analgesic and neuromodulating effect with a beneficial effect on abdominal pain, bloat, tenesmus and constipation [79].The use of antidepressants in neuropathic pain is largely diffused. The selective inhibitors of serotonin reuptake (SSRIs) are frequently used in this field, but they do not seem to have direct analgesic properties. They are adjuvant in the treatment of the

Bibliographic Reference	N. of patients	Study design	Drug dosage	Outcome measures	Results
Häuser W et al. 2012		Meta-analysis		pain, sleep, fatigue, depression and HRQOL	The SMDs of selective serotonin reuptake inhibitors (SSRIs) on pain, sleep, depression and HRQOL were significant.
Harrison et al., 1997	178	Double blind Parallel design	Fluoxetina 20 mg Placebo	MPI	Pain seriousness with fluoxetine 2.3 vs placebo 2.7. Variation from the basal line -1.4 for fluoxetine vs -0.6 for Placebo
Max, 1992	54	Crossover	Fluoxetina 20-40 mg/die Placebo	NRS	Reduction of pain score with fluoxetine 0.35 vs. placebo 0.15
Sindrup et al., 1990	26	Crossover	Paroxetina 40 mg Imipramina 25-350 mg Placebo	Pain patient reported (0-2)	Pain score with paroxetine 0.49 Pain score with imipramine 0.52 Pain score with placebo 1.47
Sindrup et al., 1992	18	Crossover	Citalopram 40 mg Placebo	Neuropathic score a 6-item	Neuropathic score with citalopram 4.5 Neuropathic score with placebo 7.0
Tack et al., 2006	23	Crossover	Citalopram 20-40 mg	SCL-90R VAS HADS	Citalopram offers a significant abdominal pain relief. Variations in score evaluation of depression or anxiety were not correlated with siymptom improvement.

Table 3: Resuming Table- SSRI, HADS: Hospital Anxiety and Depression Scale VAS: Visuo-Analogic Scale; MPI: Multidimensional Pain; SMDs: Standardized mean differences.

psychological consequences of chronic pain that strengthen and worsen the level of pain perception with fewer side effects and efficacious antidepressant effects. Some of them like citolopram, fluoxetine, fluvoxamine, paroxetine, sertraline have by far smaller collateral effects than TCA ones. Nevertheless, they can cause drowsiness, body weight variations and some memory disorders. Specifically in the treatment of diabetic neuropathy, for example, numerous studies point out SSRI should be used only in cases where TCA treatment did not have desired effects, or by those patients with coexisting depressive disorders. The guidelines for the use of antidepressants in pain related to rheumatic conditions [80] tried to reorganise the use of these drugs, in a field that, contrary to neuropathic pain, was studied little, through the analysis of 77 studies, 12 meta-analyses and numerous reviews, using evidence based approach. But they concluded that in the backache, antidepressants have a small analgesic effect, regardless of the patient's depressive state and SSRI themselves do not seem to give any benefits to the symptomatology. On the contrary, in a population of old people with arthritis and depressive disorder in co-morbidity, the improvement of depressive symptomatology caused an improvement of pain and of life quality, too. In fibromyalgia SSRI are less efficient than TCA, but they are tolerated better even when it is necessary to increase the dose in order to obtain a significant effect on pain. To sum up, according to these guidelines SSRI should be used only when TCA are not efficacious or in the case of little tolerability or rather if they are contra-indicated and with a level of evidence C-This result makes it necessary to perform further studies in order to investigate the role of plasmatic concentration, the influence of psychiatric and concomitant depressive factors and of organic lesions on the analgesic response to these drugs.

The fibromyalgia syndrome, characterized by chronic pain associated with many crippling symptoms and with high costs, was the basis of a meta-analysis of a group of German researchers, with randomized and controlled studies to evaluate antidepressant efficacy in its treatment. Eighteen randomized and controlled clinical studies with a total of 1427 participants were included. There were evidences in favor of an association between antidepressants and pain reduction, of fatigue, of depressive mood and sleep disorders. They pointed out a strong association between the use of antidepressants and the improvement of life quality correlated with health. But when they correlated the extent of the analgesic effect with the antidepressant type, it proved to be wide for TCA and tetracycle antidepressants, mean for Mao inhibitors and little for SSRI and SRNI. In conclusion, data supporting SSRI analgesic effects are limited, probably because of double role of serotonin on descendant pathways or even because some physiological mechanisms at the base of the modulation of pain expression must still be explained.

A statistically significant reduction in average pain. Average variations in score BDI-II and HADS were very small.

Significant total pain improvement: 50% of total pain improvement was independent from HAMD-17. Starting from an improvement of depression, the improvement in total pain severity was associated to higher probabilities of improvement. Duloxetine was significantly better than placebo (p<0,001) in reducing HAMD-17. Duloxetine reduced significantly physical pain symptoms compared with placebo. Patients assuming duloxetine 80 mg/day, or paroxetine 20 mg QD vs. placebo showed significantly higher reductions in the total score HADM-17. Both groups treated with duloxetine (80 and 120 mg/day) and with paroxetine showed an improvement compared with the group treated with placebo evaluated with the scales MADRS, HAMA, CGI-S, and PGI-I. Patients treated with duloxetine 80 and 120 mg/day showed a marked improvement in HADM-17 at 8 weeks. The group treated with paroxetine did not show any improvement compared with the group treated with placebo at 8 weeks. No treatment proved to be better than placebo during visits before the 8th week. Duloxetine 80 mg/day showed a significant improvement compared with placebo in the evaluation rating of scale VAS. Duloxetine was better than placebo in change on the HADM-17 Duloxetine was numerically better than fluoxetine in the primary evaluation and in most secondary evaluation Duloxetine (60 mg QD) reduced significantly the total score HADM-17 compared with placebo. Duloxetine reduced even the total pain. PGI-I and QLDS were significantly improved by duloxetine. Duloxetine was significantly better than placebo (p<0,001) in reducing the total score HAM-D-17. Duloxetine reduces significantly painful physical symptoms compared with placebo. Patients treated with duloxetine 60mg/day and duloxetine 120mg/day show a significant improvement in pain gravity compared with placebo Path analysis shows the analgesic effect of duloxetine 60 mg/day in reducing pain severity mean score. The group Duloxetine shows a significantly higher improvement in FIQ total score. Most measures of secondary outcome improved significantly in duloxetine group vs. placebo group. Duloxetine 60 mg QD and duloxetine 60 mg BID show a significantly wider improvement in BPI. There are no statistically significant

differences in the comparison between duloxetine 60 mg QD and duloxetine 60 mg BID. Duloxetine 60 mg QD is statistically better in all the measures of secondary efficacy. The primary endpoint was the reduction of pain. Both group assuming the drug once/day and the group assuming it twice/day show a significant improvement in pain intensity. Improvement in general health, fatigue and other aspects. Milnacipram: 75% of patients treated with milnacipram show an improvement compared with 38% of the group with placebo; 37% of patients treated with milnacipram twice /day show a reduction of 50% of pain intensity vs 14% of placebo group; milnacipram is associated to a significant improvement of pain, significant improvement in secondary end points, included global status

There is a significant improvement in mean pain intensity. Even the scores of anxiety and depression decreased significantly from the basal line. Variations in pain intensity are not correlated with variations in depression and anxiety.

Conclusion

By this systematic review the author's would supply to pain medicine and psychiatry a rationale to clinical practice of using the antidepressant for treating patients affected by pain conditions and depressive disorders. The great importance and the social impact of the association between pain and depression emerged from the detailed analysis of the latest literature. We pointed out how the co-morbility of the two pathologies has a negative impact on the patient's outcome with an increase of the costs relating to health expenses, a reduction of production, an increase of absence from working days and a reduction of a probable remission of depressive symptoms. We noticed how numerous brain regions are involved in both depressive disorders and pain perception: insular cortex, prefrontal cortex, anterior cingulate cortex, amygdale and hippocampus. Other studies examined the crucial role in the co-morbility of pain and depressive disorders of circulating cytokine levels: IL-&, PCR, IL-1 beta, TNF-alpha. The study group evaluated how serotonin and adrenalin are neurotransmitters involved in the physiopathology of both anxiety and depressive disorders, and therefore clinical research addressed itself to these neurotransmitters as therapeutic targets. Basing on the results of the analyzed studies, the study group suggests the following recommendations for the pain and depressive disorder treatment:

- Considering their analgesic and antidepressant effect, antidepressants can improve the symptoms and the life quality of patients with chronic pain and depressive disorder (A1).

- Tricycle antidepressants (TCA) are efficient in the treatment of chronic pain not associated with depressive disorder (A2). Otherwise, in conditions of co-morbility of chronic pain and depressive disorders there is little evidence for their efficacy (B2). Moreover, considering the high incidence of adverse events, TCA use should be limited and a therapy should always start with the lowest dosage, to titrate it later (A2).

- Concerning SNRI, the treatment with duloxetine improves the painful and depressive symptoms of patients with chronic pain (A2). It proved to be efficient even in the long term treatment (A2). Instead there are inconclusive data on the depressant and analgesic efficacy of venlafaxine in chronic pain states. (C2). Finally, Milnacipram, not yet on the market in Italy, proved to be efficient in the treatment of pain and depressive disorder, particularly in fibromyalgia (A2).

- Concerning SSRI, they have an analgesic effect independent from the antidepressant in chronic pain states (A1). Moreover, there is a certain evidence for the efficacy of SSRI in the treatment of analgesic and depressive symptoms related to the irritable bowel syndrome (IBS) (A3). Otherwise, in the states of pain caused by rheumatic pathology in co-morbility with depressive disorder, there is poor evidence for SSRI use, limiting their use only in cases where TCA are not efficient, contraindicated or with poor tolerance (C).

So only for Duloxetine there's a strong evidence for improving painful and depressive symptoms in patients with chronic pain also for long lasting therapy.

Author Contribution

CA made the data base searches and wrote the manuscript. All authors contributed to the study design and to discussion of the results.

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