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View point article

MANAGEMENT OF DEPRESSION IN THE PRESENCE OF PAIN SYMPTOMS

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SUMMARY

Somatic illness is frequently associated with depression and anxiety and major depression significantly increases risk of severe medical conditions, e.g. cardiovascular illness. One of the most frequent comorbidities is that of depression and pain. Alterations in noradrenergic and serotonergic neurotransmissions in the central nervous system have been implicated in the joint pathophysiology of depression and chronic pain. Antidepressants, alone or in combination with psychotherapy, are an effective treatment option in such cases. The newer dual action antidepressants (milnacipran, venlafaxine, duloxetine) acting specifically on both noradrenergic and serotonergic neurotransmitter systems are presumably more reliable in pain management. So far, the most extensively studied drug has been duloxetine. Twelve randomized placebo-controlled trials with the total number of 4,108 patients suffering from pain associated with major depressive disorder suggested consistent analgesic efficacy of duloxetine, especially in fibromyalgia and peripheral neuropathic pain.

Key words: *depression – pain – analgesics – anticonvulsants – antidepressants - SNRI*

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DEPRESSION AND PAIN

There is a well-established link between physical and mental illnesses, validating thus a classical medical axiom of the 'body-mind unity'. As a typical example can be taken depression, encompassing both emotional (depression, anxiety, guilt) and numerous physical (insomnia, gastro-intestinal disturbances, loss of appetite, fatigue, pain) symptoms. As Steptoe (2007) noted, there is growing evidence that depression and depressive symptoms are determinants of physical pathology.

One of the most frequent comorbidities with complex interactions is that of depression and pain. While acute pain plays a protective role in warning us of the imminent danger or damage with potentially life-threatening consequences, chronic and persisting pain serves no useful purpose (Gruener 2004). Breakthrough pain is defined as a transient exacerbation of pain of moderate-to-severe intensity, which occurs against a background of persistent pain of mild-to-moderate intensity that has been controlled (Portenoy & Hagen 1990). True breakthrough pain is either incident (predictable or unpredictable), sponta-neous (idiopathic), or end-of-dose failure (Table 1). As indicated in the table 2, the key role in the chronic pain is played by central factors (Woolf 2004). Not only painful experiences are followed by negative emotional feelings, but also chronic pain itself is a common physical complaint in people suffering from depression, persistent pain is being reported as a symptom (Van Puymbroeck et al. 2007).

Table 1. Types of pain and pain processing (adapted from Woolf, 2004 and Crofford, 2008)

	Etiology	Pain Characteristic
Nociceptive (Acute) pain	Noxious peripheral stimulus (e.g., heat, cold, intense mechanical force, chemical irritant)	Acute pain, withdrawal reflex, autonomic response
Inflammatory pain	Inflammation, tissue damage	Spontaneous pain, pain hypersensitivity (allodynia, hyperalgesia)
Neuropathic pain	Peripheral nerve damage, spinal cord injury, stroke	Spontaneous pain, pain hypersensitivity
Functional pain	Aberrant central processing	Spontaneous pain, pain hypersensitivity

A detailed literature review of the concurrent depression and pain revealed the prevalence of pain symptoms in patients with depression ranging from 15% to 100% (mean 65%) dependent on the setting (Bair et al. 2003). Prevalence of depression also varied according to the setting: among patients in pain clinics (as determined by questionnaires) was 52%, in psychiatric clinics 38%, in orthopedic or rheumatoid clinics 56%, in dental clinics treating facial pain 85%, in gynecologic clinics treating pelvic pain 13%, in population-based clinics 18%, and in primary care clinics 27%. Bair and collaborators (2003) also confirmed the fact that typical depression in primary care setting is manifested by physical complaints: more than 50% of patients with depression reported somatic complaints solely and at least 60% of these symptoms were pain-related. Presentation of physical complaints reduces recognition of depression, since physical symptoms are typically assumed to be caused by an underlying medical illness. The review demonstrated that the presence of numerous pain complaints is associated with increased severity of depression. Furthermore, higher severity of pain at baseline was predictive of poor outcome of depression and progressive pain severity at baseline results in poor depression outcomes. Overall pain and pain while awake is also one of the factors predicting insufficient response to antidepressants (Howland et al. 2008). Patients without painful physical symptoms have a better functional outcome. The presence of depression then leads to a poor treatment outcome and worse prognosis in patients treated for pain (Bair et al. 2003). A study of 186 treatment-resistant depressed patients from Sweden found that major increase in the experience pain during depression was related to increased rejection sensitivity (Ehnvall et al. 2009). A representative epidemiological survey among 12,640 adults from the Hungarian general population revealed that among those who reported pain-associated disability (32.7%), there was a 30.2% prevalence of depressive symptomatology, positively correlated with age and lower education (Réthelyi et al. 2001).

Investigation of the pathophysiological mechanisms of depressive disorder discovered numerous biological abnormalities and helped to establish a neurobiological link between emotional and physical symptoms or pain (Nemeroff 2002, Nemeroff & Vale 2005). The interplay may be mediated through the functional changes of the hypothalamic-pituitary-adrenal (HPA) axis, including corticotropin-releasing factor. The HPA system has been found to play an important role in stress response plus subsequent vulnerability and development of mood and anxiety disorders. Moreover, alterations in noradrenergic and serotonergic neurotransmissions in the central nervous system (CNS) have been implicated in the pathophysiology of both depression and chronic pain (Wise et al. 2007). Monoamines regulate mood symptoms and also modify painful sensations. Pain impulses are transmitted from the periphery to the CNS via the primary afferent fibres and can be modulated by the release of excitatory glutamate or inhibitory GABA. Descending transmissions from subcortical areas (hypothalamus, periaqueductal grey matter, raphe dorsalis, locus coeruleus) release serotonin and noradrenaline to suppress ascending painful symptoms. Pain control may thus require both serotonergic and noradrenergic descending inhibition which is the target of the dual antidepressants (tricyclics, SNRI, and also mirtazapine).

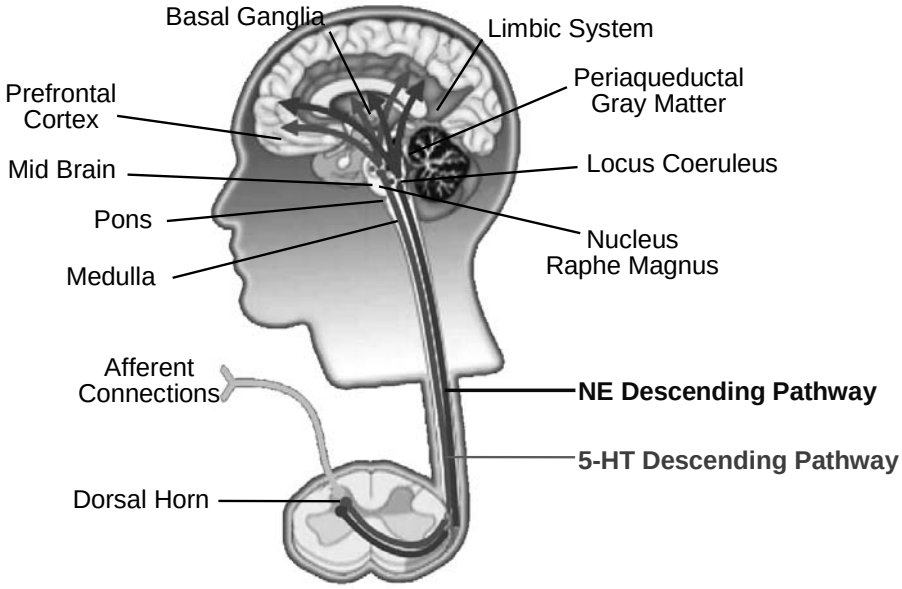

Figure 1. Serotonin and norepinephrine in the modulation of mood and pain perception

THERAPEUTICAL OPTIONS FOR PAINFUL SYMPTOMS IN DEPRESSION

Antidepressants in the management of painful symptoms

Antidepressants are universally accepted as a treatment of choice in mild, moderate, or severe depression, with or without physical symptoms (APA 2000). Although Kirsch et al. (2008) drew attention to the lack of demonstrable effect of antidepressants in mild depression, it is likely that pain in mild depression might be responding to antidepressants. Hypothesized effects of antidepressants on painful symptoms are based on the above described common pathways between depression and pain. History of using antidepressants in the management of pain dates back to the 1960's when first reports suggested that imipramine was useful in the treatment of pain in cancer patients (Mönkemeier & Steffen 1970). Since then antidepressants, mostly tricyclics, have been tested in the management of various isolated pain syndromes, including chronic back pain (Salerno et al. 2002), neuropathic pain (Saarto & Wiffen 2007), and lately in fibromyalgia (Häuser et al. 2009, Clauw 2008). Although fibromyalgia, a chronic painful medical condition of unknown etiology, is frequently associated with symptoms of depression, the syndrome itself is usually differentiated from 'depressive illness' (Arnold 2008).

Until recently, only a handful of studies investigated effects of antidepressant treatment on comorbid symptoms of pain. For example an observational study from Germany in a sample of 594 patients with comorbid depression and chronic pain found that mirtazapine, an antidepressant with combined receptor affinity, significantly reduced painful symptoms (Freynhagen et al. 2006). However, it should be noted that mirtazapine administration has been also associated with the occurrence of arthralgia (Passier & Puijenbroek 2005). This adverse event may be a consequence of the enhanced 5-HT_1-mediated neurotransmission, a mechanism shared with other antidepressants inducing arthralgia, mianserin and nefazodone.

Newer (dual acting) antidepressants modulating selectively reuptake of both serotonergic and noradrenergic neurotransmitters (SNRI) have been recently introduced into the treatment of depression and physical symptoms and conditions with comorbid depression. The rationale behind new indications is the specific action on both neurotransmitter systems implicated in the pathophysiology of pain that could hypothetically result in analgesic efficacy of the SNRI. Moreover, painkilling action of venlafaxine and mirtazapine may be partially attributed to their affinity to the opiate receptors, resulting in opioid-mediated antinociceptive effect (Schreiber et al, 2008). Analgesic effects of the SNRI were demonstrated first in animal studies of pain (e.g.,

Bardin et al. 2010), anecdotal case reports, and open trials. In the management of depression associated with pain, a prospective naturalistic Swiss community-based observational trial of 505 patients with comorbid depression and chronic pain in primary care demonstrated that three months of venlafaxine administration significantly improved both depressive and painful symptoms (Begré et al. 2008). Also duloxetine 60 mg was shown to be effective in the open treatment of painful physical symptoms in 282 patients with major depression, measured by the Brief Pain Inventory, Visual Analog Scales, and subjective instruments (Brannan et al. 2005). A small open label study investigated duloxetine 60 mg in a study sample of 30 outpatients with major depressive disorder and concurrent primary headache (chronic migraine, chronic tension-type headache, or both) (Volpe et al. 2008). Significant improvements in both headache and depression were observed already after first week of treatment and were sustained over the course of an 8-week trial. In a study of Perahia and collaborators (2009), depressed patients who were non- or partial responders to selective serotonin reuptake inhibitors (SSRI), benefited from both direct switch and a start-taper switch to duloxetine over two weeks, as evidenced by the reduction of their painful symptoms (overall pain, headache, back pain, shoulder pain).

More importantly, controlled trials yielded similar positive results. Tables 3-5 summarize all published double-blind trials of dual-acting anti-depressants in treatment of primary or secondary painful conditions, with or without depression. Most of the studies investigated effects on pain symptoms in other medical conditions, not in depression.

The data available in public domain suggests that the findings from venlafaxine studies in patients suffering from neuropathic pain, facial pain, and migraine or headache are equivocal (Table 3).

Milnacipran has been tested exclusively in fibromyalgia and the study results indicate that the response rates are modest at best (Table 4). Clinically relevant measure of effectiveness, number needed to treat (NNT) is approximately 13 in 200 mg by week 15; however, effectiveness with chronic use is questionable. In the Mease trial (2009), significant signal was lost at week 27 for both 100 mg and 200 mg strengths.

There are numerous studies investigating analgesic effects of duloxetine in fibromyalgia, neuropathic pain, and in somatic pain without comorbidity, osteoarthritis knee pain or low back pain (Table 5). Cochrane systematic review (Lunn et al, 2009) reported a moderately strong evidence indicating that duloxetine 60 mg and 120 mg daily are efficacious for treating pain in painful diabetic peripheral neuropathy in the short-term to 12-week administration with a risk ratio (RR) for 50% pain reduction at 12 weeks of 1.65 (95% confidence interval [CI] 1.34 to 2.03), NNT 6 (95% CI 5 to 10). Duloxetine at 60 mg daily is also effective in fibromyalgia over 12 weeks (RR 50% reduction in pain 1.57, 95% CI 1.20 to 2.06; NNT 8, 95% CI 5 to 17) and 28 weeks (RR 1.58, 95% CI 1.10 to 2.27). The dose of 20 mg was not found to be effective. Minor side effects were common at therapeutic doses with dose-dependent effect, but serious side effects were rare.

Moreover, duloxetine is the only dual-acting antidepressant studied in patients suffering from depression with associated painful symptoms. In two 8-week trials with total number of 641 patients, including elderly, duloxetine was superior to placebo (Brecht et al. 2007, Raskin et al. 2007). In one 9-week trial of 282 patients with major depression efficacy of duloxetine on painful symptoms failed to reach statistical significance (Brannan et al. 2005). Additional analyses suggest that effective control of pain symptoms with duloxetine may increase remission rates of depressive disorder (Fava et al. 2004, Arnold et al. 2008) and overall functional outcome (Wise et al. 2008). There are now post-hoc analyses from studies with generalized anxiety disorder available: the findings consistently suggest short- and long-term efficacy of duloxetine in control of pain symptoms in people with anxiety disorder (Beesdo et al. 2009).

Other pharmacological options

Recently published narrative review summarized available evidence and suggested stepped care approach in the pharmacological management of chronic pain, from simple analgesics, through tricyclic and dual acting antidepressants, tramadol, anticonvulsants, cyclobenzaprine, topical analgesics, to opiods (Kroenke et al. 2009).

Table 2. Double-blind trials of milnacipran in treatment of painful symptoms

Study	Drug, dosage	Study population (primary condition)	N	Study duration	Results
Gendreau et al. 2005	Milnacipran 25-200 mg/d	Predominantly female patients with fibromyalgia	125	12 weeks	–
Clauw et al. 2008	Milnacipran 100, 200 mg/d	Patients with fibromyalgia	1196	15 weeks	+
Mease et al. 2009	Milnacipran 100, 200 mg/d	Patients with fibromyalgia	888	27 weeks	+

Legend: + = statistically significant superiority of the tested compound to placebo on primary efficacy measures at endpoint; – = tested compound failed to reach/maintain superiority to placebo on primary efficacy measures at endpoint.

Table 3. Double-blind trials of venlafaxine in treatment of painful symptoms

Study	Drug, dosage	Study population (primary condition)	N	Study duration	Results
Tasmuth et al. 2002	Venlafaxine 75 mg	Patients with neuropathic pain after treatment for breast cancer	13	10 weeks (cross-over)	–
Sindrup et al. 2003	Venlafaxine 225 mg Imipramine 150 mg	Patients with painful polyneuropathy	40	3x4 weeks (cross-over)	+ *
Bulut et al. 2004	Venlafaxine 150 mg Amitriptyline 75 mg	Patients with migraine, with or without aura	52	2x12 weeks (cross-over)	*
Forsell et al. 2004	Venlafaxine 37.5-75 mg	Patients with atypical facial pain	30	2x4 weeks (cross-over)	–
Ozyalcin et al. 2005	Venlafaxine 75, 150 mg	Patients with migraine, without aura	60	2 months	+/–
Rowbotham et al. 2005	Venlafaxine 75, 150-225 mg	Type 1 or 2 DM outpatients with painful peripheral neuropathy	244	6 weeks	+
Yucel et al. 2005	Venlafaxine 75, 150 mg	Patients with neuropathic pain	60	8 weeks	–
Zissis et al. 2007	Venlafaxine 150 mg	Outpatients with tension-type headache without depression or anxiety disorder	60	12 weeks	+
Kadiroglu et al. 2008	Venlafaxine 37.5-150 mg	Type 2 DM patients with painful peripheral neuropathy	60	8 weeks	+/–

Legend: DM = diabetes mellitus; + = statistically significant superiority of the tested compound to placebo on primary efficacy measures at endpoint; – = tested compound failed to reach/maintain superiority to placebo on primary efficacy measures at endpoint; * = statistically significant improvement, non-inferiority to the active comparator.

Despite the fact that analgesics are effective treatment option for pain control, evidence of the efficacy of analgesics in patients with depression is limited. Furthermore, there are safety concerns, notably a link between opiate addiction and depression was hypothesized (Nunes et al. 2004). A tendency for overprescription of analgesics among psychiatric population was reported in a small study with 73 depressed pain patients demonstrating that opioids were administered more frequently than antidepressants (Doan & Wadden 1989). More recently, there has been a renewed interest in using opiates for treatment-resistant depression (Nyhuis et al. 2008), supported by the established anti-depressant effects of tramadol (Reeves et al. 2008).

Routinely prescribed psychotropic drugs with presumed analgesic effects are also anticonvulsants. However, a systematic review of the use of anticonvulsants for acute and chronic pain found that the data supporting analgesic effectiveness of some of them (carbamazepine) are weak (Wiffen et al. 2005). Pregabaline, together with duloxetine, is approved by the FDA for treatment of fibromyalgia and its efficacy and safety was re-confirmed in a recent meta-analysis (Straube et al. 2010). Regardless of the reviewed evidence, other anticonvulsants, including carbamazepine and more effective gabapentin, continue to be recommended for pain control, including fibromyalgia and pain with comorbid psychiatric disorders (Owen 2007, Argoff 2007).

Non-pharmacological management of painful depression

There is a solid body of evidence that psychotherapy, either alone or in combination with antidepressants, is effective in reducing the severity of physical symptoms and pain in depression. Various psychotherapeutic techniques have been used in treatment of pain patients (review in Leo et al. 2003, Molton et al. 2007). Similarly to other non-pharmacological treatment interventions, efficacy assessment of psychotherapy is hampered by the methodological shortcomings (limited sample sizes, heterogeneous groups, problematic blinding, no placebo treatment and lack of control for other variables). Nonetheless, it appears that psychotherapy can reduce some of the distress associated with pain and can promote adaptation. The most frequently utilized techniques are cognitive-behavioral therapy, operant behavioral therapy, psychodynamically oriented psychotherapy, and supportive therapies. In addition, other alternative or adjunctive methods (e.g., hypnosis, biofeedback, acupuncture, or relaxation training) may help to reduce some of the physiologic components of pain (Leo et al. 2003, Molton et al. 2007). The study of Ehnvall and collaborators (2009) discussed above suggests that successful management of painful symptoms in depression could potentially reduce rejection sensitivity.

Table 4. Double-blind trials of duloxetine in treatment of painful symptoms

Study	Drug, dosage	Study population (primary condition)	N	Study duration	Results
Arnold et al. 2004	Duloxetine 120 mg/d	Predominantly female outpatients with fibromyalgia	207	12 weeks	+/–
Arnold et al. 2005	Duloxetine 60, 120 mg/d	Female outpatients with fibromyalgia	354	12 weeks	+
Raskin et al. 2005	Duloxetine 60, 120 mg/d	Patients with diabetic peripheral neuropathic pain (caused by type 1 or 2 DM) without depression	348	12 weeks	+
Goldstein et al. 2005	Duloxetine 20, 60, 120 mg/d	Type 1 or 2 DM patients with painful peripheral neuropathy	457	12 weeks	+
Brannan et al. 2005	Duloxetine 60 mg/d	Patients with MDD	282	9 weeks	–
Brecht et al. 2007	Duloxetine 60 mg/d	Outpatients with MDD with at least moderate pain of unknown etiology	327	8 weeks	+
Raskin et al. 2007	Duloxetine 60 mg/d	Elderly patients (≥65 years, median 72) with recurrent MDD	314	8 weeks	+
Wernicke et al. 2006	Duloxetine 60, 120 mg/d	Patients with diabetic peripheral neuropathic pain (caused by type 1 or 2 DM) without depression	334	12 weeks	+
Russell et al. 2008	Duloxetine 20, 60, 120 mg/d	Patients with fibromyalgia with or without depression	520	6 months	+
Chappell et al. 2008	Duloxetine 60, 120 mg/d	Patients with fibromyalgia with or without depression	330	6 months	–
Chappell et al. 2009	Duloxetine 60, 120 mg/d	Outpatients with osteoarthritis knee pain	231	13 weeks	+
Skljarevski et al. 2009	Duloxetine 20, 60, 120 mg/d	Patients with chronic low back pain	404	13 weeks	–

Legend: DM = diabetes mellitus; MDD = major depressive disorder; + = statistically significant superiority of the tested compound to placebo on primary efficacy measures at endpoint; – = tested compound failed to reach/maintain superiority to placebo on primary efficacy measures at endpoint.

CONCLUSIONS

There is a clear link between physical symptoms and depression; somatic illnesses are frequently associated with depression and anxiety and major depression significantly increases risk of severe medical conditions (Rush 2007, Katon et al. 2007). One of the most frequent comorbidities is depression and pain. Pain severity at baseline predicts poor depression outcomes, depression results in poor treatment response and worsens prognosis in patients treated for pain. Alterations in noradrenergic and serotonergic neurotransmissions in the CNS have been implicated in the joint pathogenesis of depression and chronic pain. This paradigm is indirectly supported by the efficacy of antidepressants modulating reuptake of monoamines and serotonin in the treatment of physical and painful symptoms. The newer dual antidepressants (milnacipran, venlafaxine, duloxetine) with more specific mechanisms of action are therefore studied in controlling painful symptoms. Although some authors failed to confirm analgesic differences between antidepressants (Krebs et al. 2008), the presented overview of the published data suggests that antidepressants may differ in their efficacy and their action may be disease-specific.

Conclusions drawn from reviews and meta-analyses clearly contradict a controversial report stating that that SNRIs, particularly duloxetine, lack analgesic properties (Spielmans 2008). Duloxetine has been so far the most extensively studied drug, in twelve double-blind randomized placebo-controlled trials with the total number of 4,108 patients suffering from pain, including painful physical symptoms associated with major depressive disorder. Although a publication bias (underreporting of negative findings) cannot be completely excluded, the results are uniformly and strongly supporting evidence of analgesic efficacy of duloxetine, especially in fibromyalgia and peripheral neuropathic pain.

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